IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: US Patent No. RE39,198 Attorney Docket No. USHR-1161 US RE1

Application No. 09/712,129 Reissue Date: July 18, 2006

Original US Patent No. 5,364,866 Original Issue Date: November 15, 1994

Patentees: Joseph T. Strupczewski, Grover C. Helsley, Yulin Chiang, Kenneth J. Bordeau, and Edward J. Glamkowski

Title: Heteroarylpiperidines, pyrrolidines and piperazines and their use as antipsychotics and analgesics

Mail Stop Patent Extension

Director
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 USC 156

Pursuant to 35 USC §156 and 37 C.F.R. §§1.710-1.791, Applicant, Aventis Holdings Inc., the address of which is 3711 Kennett Pike, Greenville, Delaware, (hereinafter referred to as "Applicant,") represents that it is the owner and assignee of the entire interest in and to United States Reissued Patent No. RE39,198 (Exhibit 1, "the RE '198 patent,") granted to Joseph T. Strupczewski, Grover C. Helsley, Yulin Chiang, Kenneth J. Bordeau, and Edward J. Glamkowski (hereinafter referred to as the "Inventors") for "Heteroarylpiperidines, Pyrrolidines, and Piperazines and Their Use as Antipsychotics and Analgesics" on July 18, 2006, by virtue of an assignment from HMR Pharma, Inc. to Applicant, recorded November 29, 2007 at Reel 020174, Frame 0006.

HMR Pharma, Inc. became assignee of record by virtue of an assignment from Aventis Pharmaceuticals, Inc., recorded November 16, 2007 at Reel 020119, Frame 0606.

Aventis Pharmaceuticals, Inc. became assignee of record by virtue of a name change from Hoechst Marion Roussel, Inc. to Aventis Pharmaceuticals, Inc., the assignment recorded February 8, 2000 at Reel 010567, Frame 0944. Hoechst Marion Roussel, Inc. became assignee of record by virtue of a name change and merger, whereby Hoechst Marion Roussel Pharmaceuticals, Inc. became Hoechst Marion Roussel, Inc, the assignment recorded December 14, 1999 at Reel 010452, Frame 0703. Hoechst Marion Roussel Pharmaceuticals, Inc. became assignee of record by virtue of an assignment from the Inventors, recorded February 16, 1993 at Reel 006437, Frame 0333. (See Exhibit 2).

The RE '198 patent matured from Application No. 09/712,129, filed November 15, 2000, as an application for reissue of United States Patent No. 5,364,866 (Exhibit 3, "the '866 patent"), granted to the Inventors on November 15, 1994. The '866 patent matured from Application No. 07/969,383, filed October 30, 1992 as a continuation-in-part of Application No. 07/788,269, filed November 5, 1991, which was a continuation-in-part of Application No. 07/944,705, filed September 5, 1991, which was a continuation of Application No. 07/619,825, filed November 29, 1990, which was a continuation of Application No. 07/456,790, filed December 29, 1989 which was a continuation-in-part of Application No. 07/354,411, filed May 19, 1989.

The approved product that is relevant to this application is FANAPT™ (iloperidone) tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg, referred to herein as "FANAPT™" or "Approved Product".

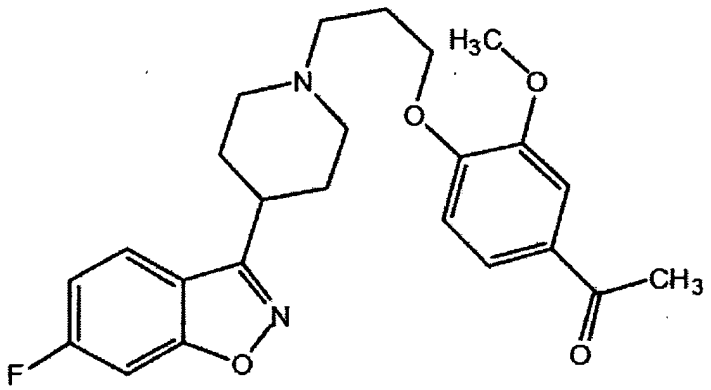
The Marketing Applicant for FANAPT™ is Vanda Pharmaceuticals, Inc. of 9605 Medical Center Drive, Suite 300, Rockville, MD, 20850. A letter on behalf of the

Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors, and affiliates is attached hereto as Exhibit 4.

The following information is submitted by Applicant, through its duly authorized attorney, in accordance with 35 U.S.C. §156 and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791, and follows the numerical format set forth in 37 C.F.R. §1.740. The undersigned is authorized to act on behalf of Applicant and proper Power of Attorney has been submitted to and accepted by the USPTO (see Exhibit 5).

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is FANAPT™ (iloperidone) tablets for oral administration. Iloperidone has the chemical name 1-[4-[3-[4-(6-flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl] ethanone. The chemical structure of iloperidone is:



FANAPT™ is the brand name for the approved product. It currently is prepared in tablet form for oral administration. There currently are seven dosage forms comprising 1, 2, 4, 6, 8, 10, or 12 mg iloperidone. In addition, each tablet currently contains the

excipients lactose monohydrate, microcrystalline cellulose, hydroxypropylmethylcellulose, crospovidone, magnesium stearate, colloidal silicon dioxide, and purified water (removed during processing).

FANAPT™ is currently approved for the treatment of schizophrenia, which is a psychotic disorder. As with other medications effective for the treatment of schizophrenia, the precise mechanism of action for the treatment of schizophrenia is unknown. (A copy of the approved labeling is attached to FDA's letter of approval, Exhibit 6).

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review period occurred:

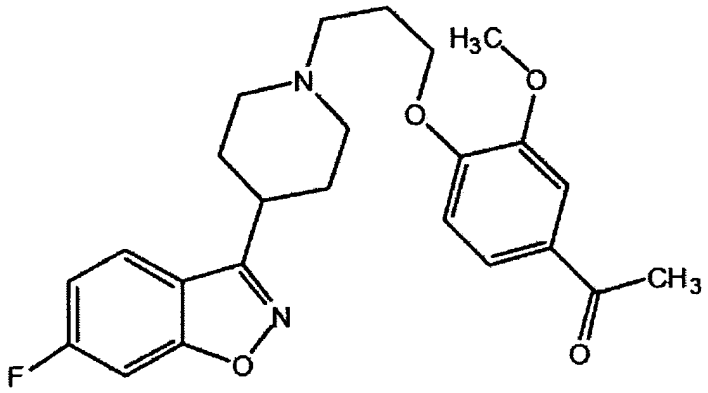
The approved product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(b)).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Regulatory approval for FANAPT™ (iloperidone) tablets, based on NDA No. 22-192, was received on May 6, 2009. A copy of the letter from FDA setting forth such approval is attached hereto as Exhibit 6.

(4) An identification of each active ingredient in the product and as to each active ingredient a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act:

The sole active ingredient in the Approved Product is iloperidone, having the chemical structure:



Neither iloperidone nor any salt or ester of iloperidone has previously been approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 CFR 1.720(f) and an identification of the date of the last day on which the application could be submitted:

This Application is timely filed, pursuant to 35 U.S.C. § 156(d)(1), within the permitted sixty-day (60-day) period that began on May 6, 2009 when the product received permission under 21 U.S.C. § 355(b) and that will expire on July 5, 2009. Applicant understands that, pursuant to 37 C.F.R. § 1.720(f), the USPTO may deem this period to expire one day earlier, on July 4, 2009.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

1. **United States Patent Number**: RE39,198
2. **Inventors**: Joseph T. Strupczewski, Grover C. Helsley, Yulin Chiang, Kenneth J. Bordeau, and Edward J. Glamkowski

3. **Date of Reissue**: July 18, 2006

4. **Expiration Date**: November 15, 2011

The expiration date of United States Reissue Patent No. RE39,198 is November 15, 2011 based on the following: the application that issued as the RE '198 patent, Application No. 09/712,129, was filed November 15, 2000 as an application for reissue of United States Patent No. 5,364,866, which originally issued November 15, 1994. Pursuant to 35 U.S.C. § 251, a reissued patent is effective for the unexpired part of the term of the original patent. The '866 patent matured from Application No. 07/969,383, filed October 30, 1992 as a continuation-in-part of Application No. 07/788,269, filed November 5, 1991, which was a continuation-in-part of Application No. 07/944,705, filed September 5, 1991, which was a continuation of Application No. 07/619,825, filed November 29, 1990, which was a continuation of Application No. 07/456,790, filed December 29, 1989 which was a continuation-in-part of Application No. 07/354,411, filed May 19, 1989. Thus, the earliest priority date for the '866 patent is May 19, 1989. The '866 patent term is the greater of 20 years from the earliest priority date and 17 years from the date of issue. The greater of these terms is 17 years from the date of issue, which is November 15, 2011. Because the '866 patent would thus have expired November 15, 2011, the RE '198 patent, which is entitled to the unexpired term of the '866 patent, will expire on November 15, 2011, in the absence of an extended term

(7) A copy of the patent for which an extension is being sought:

A copy of the patent for which extension is sought, including the entire specification and claims, is attached hereto as Exhibit 1. A copy of the original '866 patent is attached as Exhibit 3.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

United States Reissue Patent No. RE39,198 is not subject to a terminal disclaimer.

United States Reissue Patent No. RE39,198 has not been reexamined, and, thus, no reexamination certificate has been issued.

No certificates of correction have been issued for United States Reissue Patent No. RE39,198.

The first (four year) maintenance fee for the '866 patent, of which the RE '198 patent is a reissue, was paid April 30, 1998. The second (eight year) maintenance fee was paid May 3, 2002. The third (twelve year) maintenance fee was paid May 8, 2006.

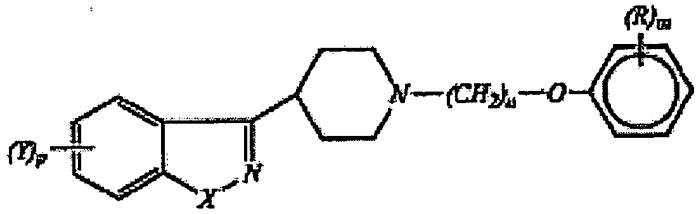
Attached as Exhibit 7 are maintenance fee records for the payment of all maintenance fees, a copy of a USPTO record showing that the 4^{th}, 8^{th}, and 12^{th} year maintenance fees have all been paid for the RE '198 patent, and a copy of a USPTO record confirming that no further fees are due. All records were downloaded from the USPTO website.

(9) A statement that the patent claims the approved product, a method of using the approved product, or a method of manufacturing the approved product and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product, method of using the approved product, or method of manufacturing the approved product:

The patent claims the approved product and a method of using the approved product. Specifically, claims 1, 3, 70, 71, 72, 73, 77, 82 and 83 claim the approved product and claim 84 claims a method of using the approved product.

Pursuant to 37 C.F.R. § 1.740(a)(9), a showing which demonstrates the manner in which one product claim and one method of use claim read on the approved product and method of using the approved product is set forth herein below.

Claim 1 claims a compound having the following structure:



Said structure is iloperidone, the active ingredient in FANAPT™ (iloperidone) tablets, when:

- X is –O-, as recited at column 111, line 38;
- p is 1, as recited at column 111, line 39;
- Y is fluorine (specifically, 6-fluoro), as recited at column 111, line 40;
- n is 3, as recited at column 111, line 46;
- R is lower alkoxy (specifically, 3-methoxy (see column 13, lns. 39-42 & 47-50)) and –C(O)-alkyl (specifically, 1-ethanone) , as recited at column 111, line 66 and column 112, line 5; and
- m is 2.

Claim 84 claims a method of treating psychoses that comprises administering to a mammal a psychoses-treating effective amount of a compound as claimed in any one of claims 1-75 and 77-81 (see column 119, lines 32-35). FANAPT™ (iloperidone) tablets are a drug product approved under section 505(b) of the FFDCA which has iloperidone as the active pharmaceutical ingredient and which is indicated for the treatment of schizophrenia. Schizophrenia is a psychotic condition, and iloperidone is a compound of claims 1, 3, 70, 71, 72, 73, and 77. Accordingly, Claim 84 reads on a method of using the approved drug product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. §156(g)

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the Investigational New Drug application (IND) and the IND number, the date on which a New Drug Application (NDA) or a Product License Application (PLA) was initially submitted, and the NDA or PLA number; and the date on which the NDA was approved or the Product License Issued

An original investigational new drug application ("IND") was filed on April 25, 1991, and assigned IND No. 36,827. A copy of the letter acknowledging receipt of the IND on May 1, 1991 is attached as Exhibit 8. Accordingly, IND No. 36,827 became effective 30 days from May 1, 1991, which is May 31, 1991.

A new drug application ("NDA") was submitted on September 27, 2007 and acknowledged as received on September 27, 2007, in an email from FDA dated September 27, 2007. (Exhibit 9). The NDA number assigned to the application for iloperidone was 22-192. Accordingly, the NDA was initially submitted on September 27, 2007. The NDA was approved on May 6, 2009. (Exhibit 6).

[CONTINUED ON NEW PAGE]

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

In accordance with 37 C.F.R. § 1.740(a)(11), a list of communications between the FDA and the Marketing Applicant, its predecessor, and affiliates, in IND No. 36,827 and NDA No. 22-192 during the applicable regulatory review period with respect of the approved product is provided at Exhibits 10 & 11.

The original sponsor of IND No. 36,827 was Hoechst-Roussel Pharmaceuticals, Inc., indicated in the Exhibit 10 as "HMR." Following a series of mergers, HMR is succeeded by Sanofi-Aventis SA. Applicant, the owner of the patent for which term extension is herein requested, is an affiliate of Sanofi-Aventis SA.

Clinical trials were begun shortly following acceptance of the IND. The first clinical trial report was submitted on or about March 25, 1993. An End of Phase II meeting with the FDA was held on or about October 17, 1995, although there was at least one subsequent Phase II study. The first Phase III protocol was submitted to the IND on Sept 24, 1998.

By agreement effective December 31, 1996, the right to develop and commercialize iloperidone was granted by HMR to Titan Pharmaceuticals, Inc., which thereafter became the sponsor of the IND.

By agreement effective November 20, 1997, the right to develop and commercialize iloperidone was granted by Titan Pharmaceuticals to Novartis Pharmaceuticals, Inc., which thereafter became the sponsor of the IND.

By agreement effective June 4, 2004, the right to develop and commercialize iloperidone was granted by Novartis Pharmaceuticals, Inc. to Vanda, which thereafter became the sponsor of the IND and, subsequently, of NDA No. 22-192.

Subsequent to the Vanda-Novartis agreement, development of iloperidone was undertaken by Vanda through NDA approval on May 6, 2009. The NDA was found to be non-approvable by the FDA by letter dated July 25, 2008. Thereafter, Vanda re-analyzed the data submitted with the NDA in the light of the reasons given by the FDA for non-approval and on August 21, 2008 submitted a briefing document to the FDA summarizing the results of the re-analysis and addressing the reasons for non-approval. Representatives of Vanda met with the FDA on September 10, 2008 and filed a complete response to all issues on or about November 6, 2008. FDA then notified Vanda that the complete response was accepted on November 19, 2008 and set a new decision date of May 6, 2009. From November 19, 2008 through approval on May 6, 2009, Vanda replied to multiple queries from the FDA.

[CONTINUED ON NEW PAGE]

(12) A statement that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed including how the length of extension was determined:

(a) Statement of the eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(1) Pursuant to 35 U.S.C. §154 and 35 U.S.C. §251, and for reasons discussed above, the term of United States Patent No. RE39,198 is currently set to expire on November 15, 2011. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. RE39,198.

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This application is being submitted by Applicant, Aventis Holdings, Inc., the owners of record of United States Patent No. RE39,198. (See Exhibit

2). Aventis Holdings, Inc. is the owner of record by virtue of duly recorded assignments discussed above. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on May 6, 2009, the date the product received permission for marketing under Section 505 of the FFDCA [21 U.S.C. §355], and ending on July 5, 2009. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the May 6, 2009 letter from the FDA to Marketing Applicant Vanda Pharmaceuticals, Inc., submitted as Exhibit 6, the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of the FANAPT™ (iloperidone) product is the first permitted commercial marketing and use under Section 505 of the FFDCA [21 U.S.C. §355] of the product, as defined in 35 U.S.C. § 156(f). (See Section 4, above).

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. RE39,198, now expiring November 15, 2011, should be extended to November 15, 2016, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of IND No. 36,827 of May 31, 1991 and the submission of the NDA 22-192 on September 27, 2007 (i.e., the "testing phase"), a period of 5,963 days, plus the length of time between the submission of the NDA No. 22-

192 on September 27, 2007 to NDA approval on May 6, 2009 (i.e., the "approval phase"), a period of 587 days. These two periods added together equal 6,550 days.

Pursuant to 37 C.F.R. § 1.775(d), the term of the patent as extended is determined by subtracting from the 6,550 day regulatory review period the following:

(i) 1,264 days, which is the number of days in the IND and NDA periods on or before the issuance of original United States Patent No. 5,364,866 on November 15, 1994. While not believed necessary to this calculation, please note that the original '866 patent would have been eligible for extension, but for the reissue. And

(ii) 2,349 days, which is one-half the number of days remaining in the IND period after the subtraction of 1,264 days above (wherein half days are ignored for purposes of this subtraction, as provided by 37 C.F.R. § 1.775(d)(1)(iii)).

From the foregoing calculation, an extension of 2,936 days results, i.e., the remaining period under 35 U.S.C. 156(g)(1)(B)(i) (2,349 days) plus the remaining period under 35 U.S.C. §156(g)(1)(B)(ii) (587 days). This length of an extension would provide a new expiration date for U.S. Patent No. RE38,198 of November 29, 2019. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted. In this case, since the current expiry date of U.S. Patent No. RE39,198 is November 15, 2011, no patent term extension could extend the term of the patent beyond November 15, 2016. Consequently, this provision limits the possible extension available to U.S. Patent RE39,138 to November 15, 2016.

Second, under 35 U.S.C. §156(c)(3), if the calculated extension period would lead to a patent term that would result in a patent term exceeding 14 years after the

date of approval, that is, a patent term expiring after May 6, 2023, the period of extension would be limited so that this period does not exceed 14 years. In this case, this provision does not operate to limit the possible extension available to U.S. Patent No. RE39,198.

Accordingly, United States Patent No. RE39,198 is eligible for the maximum five year extension allowable under 35 U.S.C. §156(g)(6)(A).

(13) A statement that Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought (See 37 C.F.R. §1.765)

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (See 37 C.F.R. §1.20(j))

The Director is hereby authorized to charge any fees due to this submission to our Deposit Account No. **18-1982**, under Docket No. USHR-1161 US REI1, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned. A duplicate of this Request (without Exhibits 1 to 11) is attached.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Dr. Balaram Gupta
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US Patent Operations
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3364
Telefax: 908-231-2626

Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156, including Exhibits **1-11**, is accompanied by two additional copies, for a total submission of three copies.

Dated: June 9, 2009

Respectfully submitted,

By Balaram Gupta
Balaram Gupta, Ph. D., J. D.
Registration No. 40,009
Attorney for Applicants

List of Exhibits Attached:

Exhibit 1	A copy of the US Patent No. RE39,198 for which extension is sought
Exhibit 2	A copy of the Patent Assignment Abstract
Exhibit 3	A copy of US Patent No. 5,364,866
Exhibit 4	A letter of authorization from the NDA Holder, Vanda Pharmaceuticals
Exhibit 5	A copy of the Notice of Acceptance of Power of Attorney
Exhibit 6	A copy of the NDA Approval Letter from the FDA
Exhibit 7	A copy of Patent Maintenance Fees Statement
Exhibit 8	A letter of acknowledgment of IND Submission
Exhibit 9	An e-mail copy of acknowledgement of NDA
Exhibit 10	Listing of the IND Events
Exhibit 11	Listing of the NDA Events

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US00RE39198E

EXHIBIT 1

(19) **United States**

(12) **Reissued Patent**

Strupczewski et al.

(10) **Patent Number: US RE39,198 E**

(45) **Date of Reissued Patent: Jul. 18, 2006**

(54) **HETEROARYLPIPERIDINES, PYRROLIDINES AND PIPERAZINES AND THEIR USE AS ANTIPSYCHOTICS AND ANALGESICS**

(75) Inventors: **Joseph T. Strupczewski**, Flemington, NJ (US); **Grover C. Helsley**, Rosemont, NJ (US); **Yulin Chiang**, Convent Station, NJ (US); **Kenneth J. Bordeau**, Kintnersville, PA (US); **Edward J. Glamkowski**, Warren, NJ (US)

(73) Assignee: **Aventis Pharmaceuticals Inc.**, Bridgewater, NJ (US)

(21) Appl. No.: **09/712,129**

(22) Filed: **Nov. 15, 2000**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,364,866**
Issued: **Nov. 15, 1994**
Appl. No.: **07/969,383**
Filed: **Oct. 30, 1992**

U.S. Applications:

(63) Continuation-in-part of application No. 07/788,269, filed on Nov. 5, 1991, now abandoned, which is a continuation-in-part of application No. 07/944,705, filed on Sep. 5, 1991, now abandoned, which is a continuation of application No. 07/619,825, filed on Nov. 29, 1990, now abandoned, which is a continuation of application No. 07/456,790, filed on Dec. 29, 1989, now abandoned, which is a continuation-in-part of application No. 07/354,411, filed on May 19, 1989, now abandoned.

(51) **Int. Cl.**

A61K 31/445	(2006.01)
A61K 31/495	(2006.01)
A61K 31/42	(2006.01)
C07D 211/00	(2006.01)

(52) **U.S. Cl.** **514/321**; 514/254.02; 514/254.06; 514/318; 514/322; 514/373; 514/379; 514/403; 544/257; 544/366; 544/368; 546/194; 546/198; 546/199; 546/270.1; 546/271.7; 548/207; 548/356.5

(58) **Field of Classification Search** 514/318, 514/321, 322; 546/194, 198, 199
See application file for complete search history.

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* cited by examiner

Primary Examiner—Brenda Coleman
(74) *Attorney, Agent, or Firm*—Synnestvedt & Lechner LLP

(57) **ABSTRACT**

Heteroarylpiperidines, pyrrolidines, and piperazines are useful as antipsychotic and analgesic agents. The compounds are especially useful for treating psychoses by administering to a mammal a psychoses-treating effective amounts of one of the compounds. The compounds are also useful as analgesics by administering a pain-relieving effective amount of one of the compounds to a mammal.

146 Claims, No Drawings

HETEROARYLPIPERIDINES, PYRROLIDINES AND PIPERAZINES AND THEIR USE AS ANTIPSYCHOTICS AND ANALGESICS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 788,269, filed Nov. 5, 1991 (Attorney Docket No. 02489-0028-03000), now abandoned, which is a continuation-in-part of application Ser. No. 944,705, filed Sep. 5, 1991 (Attorney Docket No. 02489-0028-04000), now abandoned, which is a continuation of application Ser. No. 619,825, filed Nov. 29, 1990 (Attorney Docket No. 02489-0028-02000), now abandoned, which is a continuation of application Ser. No. 456,790, filed Dec. 29, 1989 (Attorney Docket No. 02489-0028-01000), now abandoned, which is a continuation-in-part of application Ser. No. 354,411, filed May 19, 1989, (Attorney Docket Nos. 02489-0028-00000 and HR-1161), now abandoned. The entire disclosure of these applications is relied upon and incorporated by reference herein.

BACKGROUND OF THE INVENTION

This invention relates to heteroarylpiperidines, pyrrolidines and piperazines. More particularly, this invention relates to heteroarylpiperidines, pyrrolidines and piperazines having antipsychotic activity and to their use as antipsychotic drugs.

The therapeutic treatment of schizophrenic patients by administration of neuroleptic drugs, such as chlorpromazine, haloperidol, sulpiride, and chemically closely related compounds, is widespread. While control of schizophrenic symptoms has been successful, treatment with these drugs does not cure the psychotic patient, who will almost certainly relapse if medication is discontinued. There exists a continuing need in the art for antipsychotic drugs for the treatment of psychoses.

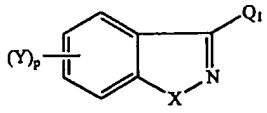
Moreover, some of the known neuroleptics produce unwanted side effects. For example, the side effects of many antipsychotic drugs include the so-called extrapyramidal symptoms, such as rigidity and tremor, continuous restless walking, and tardive dyskinesia which causes facial grimacing, and involuntary movements of the face and extremities. Orthostatic hypotension is also common. Thus, there also exists a need in the art for antipsychotic drugs that produce fewer or less severe manifestations of these common side effects.

Moreover, there has been a need for drugs that can produce other biological effects. For example, relief from pain has been an age-old aspiration which has led to the discovery of natural and synthetic analgetics. Nevertheless, the need for safe and effective analgetics has continued to the present day.

SUMMARY OF THE INVENTION

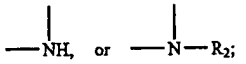
This invention aids in fulfilling these needs in the by providing a compound of the formula:

(I)



wherein

X is —O—, —S—,



R_2 is selected from the group consisting of lower alkyl, aryl lower alkyl, aryl, cycloalkyl, aroyl, alkanoyl, and phenylsulfonyl groups;

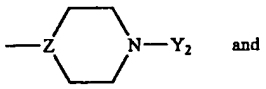
p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—;

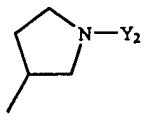
Q_1 is selected from the group consisting of:

(a)

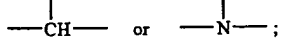


and

(b)



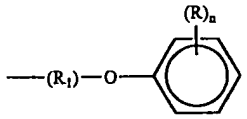
where Z is



and

Y_2 is selected from the group consisting of:

(1)



in which (R_1) is $—(CH_2)_n—$ where n is 2, 3, 4, or 5; or

$—CH_2—CH=CH—CH_2—$,

$—CH_2—C\equiv C—CH_2—$,

$—CH_2—CH=CH—CH_2—CH_2—$,

$—CH_2—CH_2—CH=CH—CH_2—$,

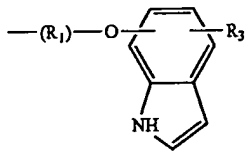
$—CH_2—C\equiv C—CH_2—CH_2—$, or

$—CH_2—CH_2—C=C—CH_2—$,

the —CH=CH— bond being cis or trans; and

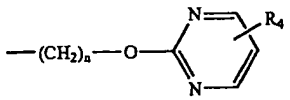
R and m are as defined hereinafter;

(2)

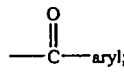


where R_3 is H or —OCH_3 and n has the above meaning;

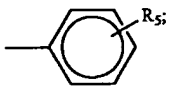
(3)



R_4 is hydrogen, lower alkyl, lower alkoxy, amino, mono- or dialkylamino, C_1–C_3 acyl amino, C_1–C_6 alkanoyl, trifluoromethyl, chlorine, fluorine, bromine,



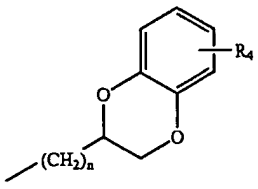
in which aryl is phenyl or



where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;

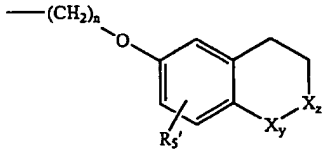
where n has the above meaning;

(4)



where n and R_4 are as previously defined;

(5)



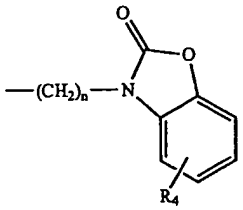
where either one of X_y or X_z is

and the other is —CH_2—;

and

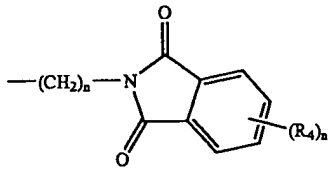
R_5' is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, or bromine; and

(6)



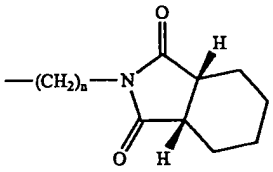
where n and R_4 are as previously defined;

(7)



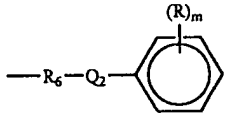
where n and R_4 are as previously defined;

(8)



where n is as previously defined;

(9)



where Q_2 is S, NH, or —CH_2—;

R_6 is the same as R_1 when Q_2 is S or NH; and

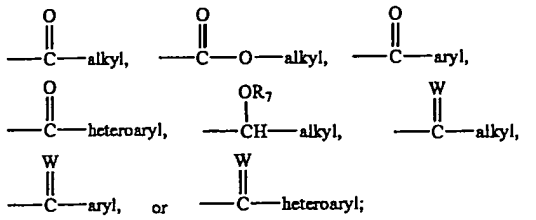
when Q_2 is —CH_2—, R_6 is selected from the group consisting of:

—CH_2—CH_2—
—CH_2—CH_2—CH_2—
—CH_2—CH_2—CH_2—CH_2—
—CH_2—CH=CH—CH_2—
—CH_2—CH_2—CH=CH—
—CH_2—CH=CH—CH_2—
—CH_2—CH_2—CH=CH—
—CH_2—CH=CH—CH_2—CH_2—
—CH_2—CH_2—CH=CH—CH_2—
—CH_2—CH_2—CH_2—CH=CH—
—CH_2—CH=CH—CH_2—CH_2—
—CH_2—CH_2—CH=CH—CH_2—
—CH_2—CH_2—CH_2—CH=CH—
—CH_2—C≡C—CH_2
—CH_2—CH_2—C≡C—
—CH_2—C≡C—CH_2—CH_2—
—CH_2—CH_2—C≡C—CH_2—
—CH_2—CH_2—CH_2—CH_2—C≡C—

the —CH=CH— bone being cis or trans;

R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio,

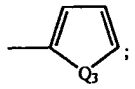
trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, dialkylaminocarbonyl, formyl,



alkyl is lower alkyl;

aryl is as previously defined;

heteroaryl is



Q_3 is —O—, —S—, —NH, —CH=N;

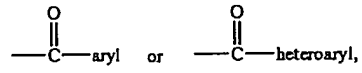
W is CH_2 or CHR_8 or N—R_9;

R_7 is hydrogen, lower alkyl, or acyl;

R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and

R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,

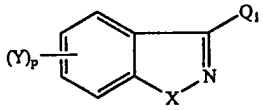


where aryl and heteroaryl are as defined above; and

m is 1, 2, or 3;

or a pharmaceutically acceptable acid addition salt thereof.

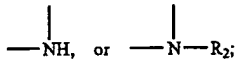
This invention also aids in fulfilling these needs the art by providing a compound of the formula:



(I)

wherein

X is —O—, —S—,



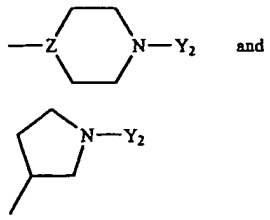
R_2 is selected from the group consisting of lower alkyl, aryl lower alkyl, aryl, cycloalkyl, aroyl, alkanoyl, and phenylsulfonyl groups;

p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

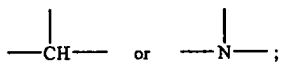
Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—;

Q_1 is selected from the group consisting of:



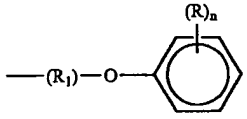
(a) and (b)

where Z is



and

Y_2 is selected from the group consisting of:



(1)

in which (R_1) is R_{20}, R_{21} or R_{22}, wherein:

R_{20} is —$(CH_2)_n$— where n is 2, 3, 4 or 5;

R_{21} is

—CH_2—CH=CH—CH_2—,

—CH_2—C≡C—CH_2—,

—CH_2—CH=CH—CH_2—CH_2—,

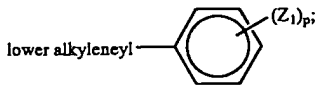
—CH_2—CH_2—CH=CH—CH_2—,

—CH_2—C≡C—CH_2—CH_2—, or

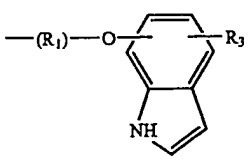
—CH_2—CH_2—C≡C—CH_2—,

the —CH=CH— bond being cis or trans;

R_{22} is R_{20} or R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one C_1–C_6 linear alkyl group, phenyl group or



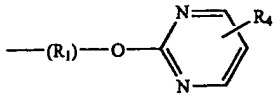
where Z_1 is lower alkyl, —OH, lower alkoxy, —CF_3, —NO_2, —NH_2 or halogen; and R and m are as defined hereinafter;



(2)

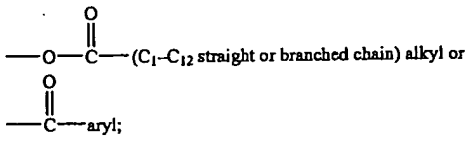
where R_1 is as previously defined, and R_3 is hydrogen or —OCH_3;

(3)

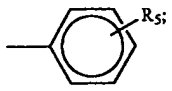


where R_1 is as previously defined; and

R_4 is hydrogen, lower alkyl, lower alkoxy, hydroxy, amino, mono- or dialkylamino, C_1–C_3 acyl amino, C_1–C_6 alkanoyl, trifluoromethyl, chlorine, fluorine, bromine,

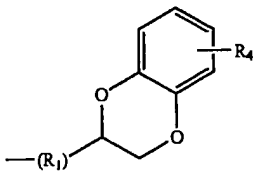


in which aryl is phenyl or



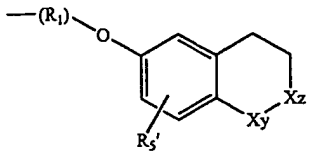
where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;

(4)



where R_1 and R_4 are as previously defined;

(5)



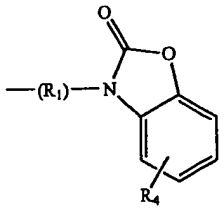
where either one of X_y or X_z is

and the other is —CH_2—; and

R_5' is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, or bromine; and

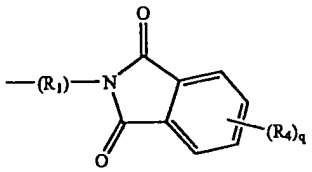
R_1 is as previously defined;

(6)



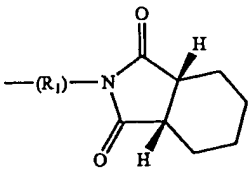
where R_1 and R_4 are as previously defined;

(7)



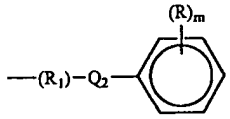
where q is 1, 2, 3 or 4, and R_1 and R_4 are as previously defined;

(8)



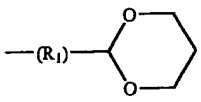
where R_1 is as previously defined;

(9)



where R_1 is as previously defined;
Q_2 is S, NH, or —CH_2—; and
R and m are as defined hereinafter;

(10)

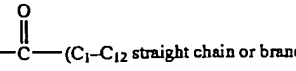


where R_1 is as previously defined;

(11)

—R_1—O—R_{12}

where R_{12} is selected from the group consisting of: hydrogen,



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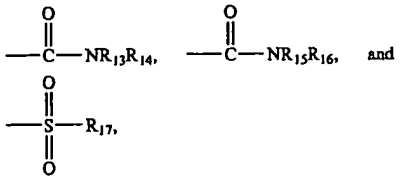


where R_{13} is selected from the group consisting of hydrogen and (C_1–C_{12}) alkyl groups;

where R_{14} is selected from the group consisting of hydrogen and (C_1–C_{12}) alkyl groups;

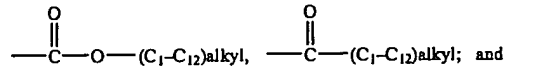
where $NR_{15}R_{16}$ taken together form a ring structure selected from the group consisting of piperidinyl, morpholinyl and piperazinyl;

where R_{17} is selected from the group consisting of lower alkyl and aryl groups;

where R_{18} and R 19 are independently selected from the group consisting of:

hydrogen,

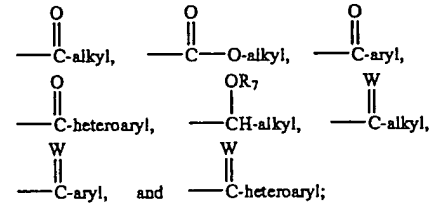
(C_1–C_{12} straight or branched chain) alkyl,



where $NR_{18}R_{19}$ taken together form a ring structure selected from the group consisting of piperidinyl, morpholinyl and piperazinyl;

where R_1 and R12 are as previously defined;

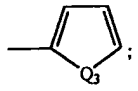
R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, formyl,



alkyl is lower alkyl;

aryl is as previously defined;

heteroaryl is



Q_3 is —O—, —S—,

—CH=N—;

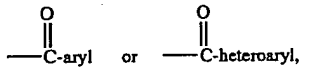
W is CH_2 or CHR_8 or N—R_9;

R_7 is hydrogen, lower alkyl, or acyl;

R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and

R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,



where aryl and heteroaryl are as defined above; and

m is 1, 2, or 3;

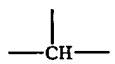
with the proviso that in formula (9) Z is not

when X is —S—, Q_2 is —CH_2—, Y is hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, or trifluoromethyl, and p is 1 or 2;

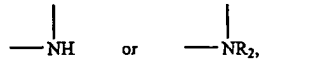
with the proviso that in formula (4) R_4 is not H when R_1 is R_{20}, Z is not

X is —S—, Y is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or trifluoromethyl, and p is 1 or 2;

with the proviso that in formula (9) Z is not



when X is

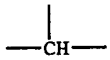


Y is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or trifluoromethyl and Q_2 is —CH_2—;

with the proviso that in formula (9) Z is not

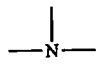
when X is —O—, Q_2 is —CH_2—, Y is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen, and p is 1 or 2;

with the proviso that in formula (9) Z is not

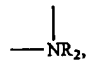


when X is —S—, Q_2 is —CH_2—, Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2, R is hydrogen, and m is 1;

with the proviso that in formula (9) Z is not



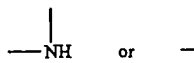
when X is



Q_2 is —CH_2—, R is chlorine, fluorine, bromine, iodine, lower alkyl, lower alkoxy, lower alkyl thio, lower mono- or dialkylamino, amino, cyano, hydroxy, trifluoromethyl; R_2 is aryl; Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2;

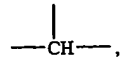
with the proviso that in formula (9) Z is not

when X is



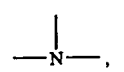
where R_2 is lower alkyl, aryl lower alkyl, or phenylsulfonyl, Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2 and Q_2 is —CH_2—;

with the proviso that Y_2 is not the moiety of formula (8) when Z is



X is O, p is 1, and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

with the proviso that in formula (1) Z is not

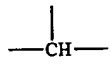


where X is O or S, Y is hydrogen, R is hydrogen, C_1–C_4 alkyl, chlorine, fluorine, bromine, iodine, cyano, C_1–C_4alkoxy, aryl, —$COOR_{23}$ where R_{23} is C_1–C_4 alkyl;

with the proviso that in formula (1) Z is not

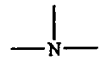
when X is —S—, R_1 is R_{20}, R is H, and m=1;

with the proviso that in formula (7) R_4 is not hydrogen when Y is 6-F, X is —O—, Z is

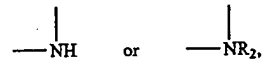


and n is 2, 3 or 4;

with the proviso that in formula (11) R_{12} is not H when Z is



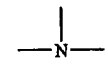
X is



where R_2 is lower alkyl, aryl lower alkyl, or phenylsulfonyl Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group and p is 1 or 2;

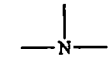
with the proviso that in formula (11), R_{12} is not H when X is

where R_2 is phenyl, Z is



and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

with the proviso that in formula (12), R_{18} and R_{19} are not lower alkyl when Z is



X is

and R_2 is aryl and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

with the proviso that in formula (12), when X is —O—, Z is

and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group, R_{18} and R_{19} are not lower alkyl;

with the proviso that in formula (12), R_{18} and R_{19} are not hydrogen when R_1 is R_{20}, Z is

X is —O—, and Y is 6-F;

all geometric optical and stereoisomers thereof, or a pharmaceutically acceptable acid addition salt thereof

This invention also provides a pharmaceutical composition, which comprises a compound of the invention and a pharmaceutically acceptable carrier therefor. In one embodiment of the invention, the pharmaceutical composition is an antipsychotic composition comprising a compound of the invention in an amount sufficient to produce an antipsychotic effect.

In addition, this invention provides a method of treating psychoses, which comprises administering to a patient a pharmaceutically effective amount of a compound of the invention.

Finally, this invention provides a method of alleviating pain by administering to a patient a pain-relieving amount of a compound of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The compounds of this invention are useful as antipsychotic drugs and as analgesic agents. The compounds of the invention can contain a variety of different substituents and chemical groups. As used herein, when the term "lower" is mentioned in connection with the description of a particular group, the term means that the group it is describing contains from 1 to 6 carbon atoms.

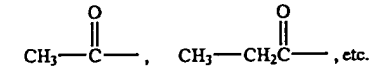
The term "alkyl" as used herein refers to a straight or branched chain hydrocarbon group containing no unsaturation, for example, methyl, ethyl, isopropyl, 2-butyl, neopentyl, or n-hexyl.

The term "alkoxy" as used herein refers to a monovalent substituent comprising an alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen, e.g. methoxy, ethoxy, propoxy, butoxy, or pentoxy.

The term "alkylene" as used herein refers to a bivalent radical of a lower branched or unbranched alkyl group having valence bonds on two terminal carbons thereof, for example, ethylene (—CH_2CH_2—), propylene (—$CH_2CH_2CH_2$—), or isopropylene

The term "cycloalkyl" refers to a saturated hydrocarbon group possessing at least one carbocyclic ring, the ring containing from 3 to 10 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclodecyl and the like.

The term "alkanoyl" refers to the radical formed by removal of the hydroxyl function from an alkanoic acid. More particularly, the term "alkanoyl" as used herein refers to an alkyl carbonyl moiety containing from 2 to 11 carbon atoms, e.g.



Examples of alkanoyl groups are formyl, acetyl, propionyl, 2,2-dimethylacetyl, hexanoyl, octanoyl, decanoyl, and the like.

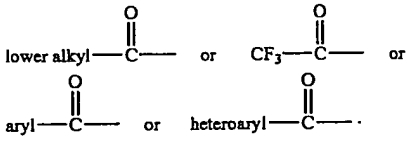
The term "alkanoic acid" refers to a compound formed by combination of a carboxyl group with a hydrogen atom or alkyl group. Examples of alkanoic acids are formic acid, acetic acid, propanoic acid, 2,2-dimethylacetic acid, hexanoic acid, octanoic acid, decanoic acid, and the like.

The term "aryl lower alkyl" refers to compounds wherein "aryl" and "loweralkyl" are as defined above.

The term "lower alkylthio" refers to a monovalent substituent having the formula lower alkyl—S—.

The term "phenylsulfonyl" refers to a monovalent substituent having the formula phenyl-SO_2—.

The term "acyl" refers to a substituent having the formula



The term "lower monoalkylamino" refers to a monosubstituted derivative of ammonia, wherein a hydrogen of ammonia is replaced by a lower alkyl group.

The term "lower dialkylamino" refers to a disubstituted derivative of ammonia, wherein two hydrogens of ammonia are replaced by lower alkyl groups.

The term "acylamino" refers to a primary or secondary amine, wherein a hydrogen of the amine is replaced by an acyl group, where acyl is as previously defined.

The term "dialkylaminocarbonyl" refers to a derivative of an acid, wherein the hydroxyl group of the acid is replaced by a lower dialkylamino group.

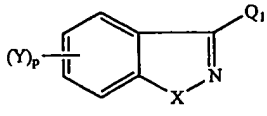
The term "aroyl" refers to a disubstituted carbonyl, wherein at least one substituent is an aryl group, where "aryl" is as previously defined.

Unless otherwise indicated, the term "halogen" as used herein refers to a member of the halogen family selected from the group consisting of fluorine, chlorine, bromine, and iodine.

Throughout the specification and appended claims, a given chemical formula or name shall encompass all geometric, optical and stereoisomers thereof where such isomers exist.

A. COMPOUNDS OF THE INVENTION

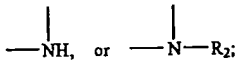
The compounds of this invention can be represented by the following formula:



(I)

wherein

X is —O—, —S—,



R_2 is selected from the group consisting of lower alkyl, aryl lower alkyl, aryl, cycloalkyl, aroyl, alkanoyl, and phenylsulfonyl groups;

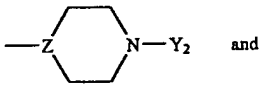
p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—;

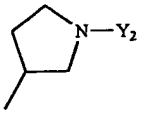
Q_1 is selected from the group consisting of:

(a)

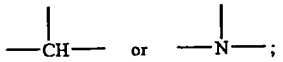


and

(b)



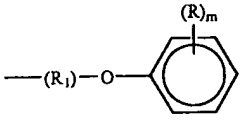
where Z is



and

Y_2 is selected from the group consisting of:

(1)



in which (R_1) is R_{20}, R_{21} or R_{22}, wherein

R_{20} is $—(CH_2)_n—$ where n is 2, 3, 4 or 5;

R_{21} is

$—CH_2—CH=CH—CH_2—$,

$—CH_2—C\equiv C—CH_2—$,

$—CH_2—CH=CH—CH_2—CH_2—$,

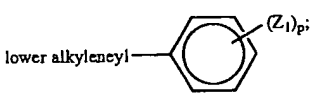
$—CH_2—CH_2—CH=CH—CH_2—$,

$—CH_2—C\equiv C—CH_2—CH_2—$, or

$—CH_2—CH_2—C\equiv C—CH_2—$,

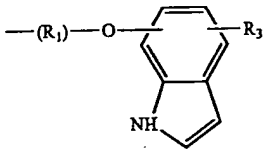
the —CH=CH— bond being cis or trans;

R_{22} is R_{20} or R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one C_1–C_6-linear alkyl group, phenyl group or



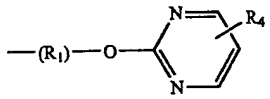
where Z_1 is lower alkyl, —OH, lower alkoxy, $—CF_3$, $—NO_2$, $—NH_2$ or halogen; and R and m are as defined hereinafter;

(2)



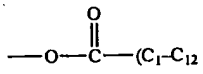
where R_1 is as previously defined, and R_3 is hydrogen or $—OCH_3$;

(3)

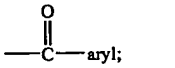


where R_1 is as previously defined; and

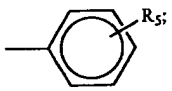
R_4 is hydrogen, lower alkyl, lower alkoxy, hydroxy, amino, mono- or dialkylamino, C_1–C_3 acyl amino, C_1–C_6 alkanoyl, trifluoromethyl, chlorine, fluorine, bromine,



straight or branched chain) alkyl or

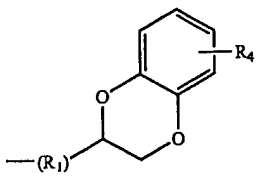


in which aryl is phenyl or

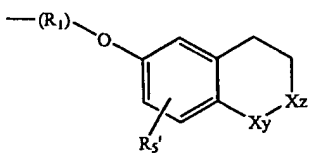


where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;

(4)



where R_1 and R_4 are as previously defined;



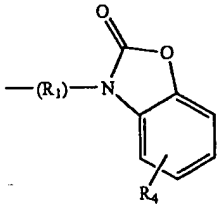
where either one of X_y or X_z is

and the other is —CH_2—; and

R_5' is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, or bromine; and

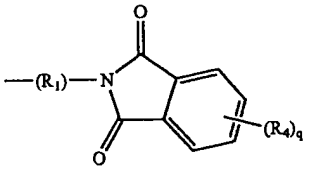
R_1 is as previously defined;

(6)



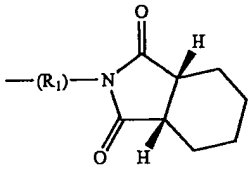
where R_1 and R_4 are as previously defined;

(7)



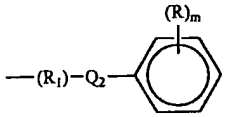
where q is 1, 2, 3 or 4, and R_1 and R_4 are as previously defined;

(8)



where R_1 is as previously defined;

(9)

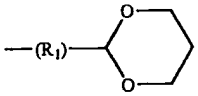


where R_1 is as previously defined;

Q_2 is S, NH, or —CH_2—; and

R and m are as defined hereinafter;

(10)

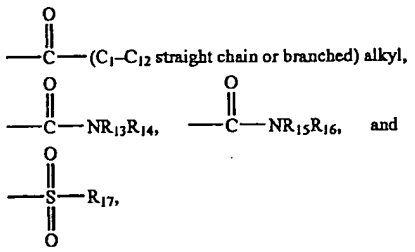


where R_1 is as previously defined;

—R_1—O—R_{12} (12)

where R_{12} is selected from the group consisting of:

hydrogen,



where R_{13} is selected from the group consisting of hydrogen and (C_1–C_{12}) alkyl groups;

where R_{14} is selected from the group consisting of hydrogen and (C_1–C_{12}) alkyl groups;

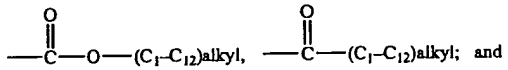
where $NR_{15}R_{16}$ taken together form a ring structure selected from the group consisting of piperidinyl, morpholinyl and piperazinyl;

where R_{17} is selected from the group consisting of lower alkyl and aryl groups;

—R_1—$NR_{18}R_{19}$ (12)

where R_{18} and R_{19} are independently selected from the group consisting of:

hydrogen,

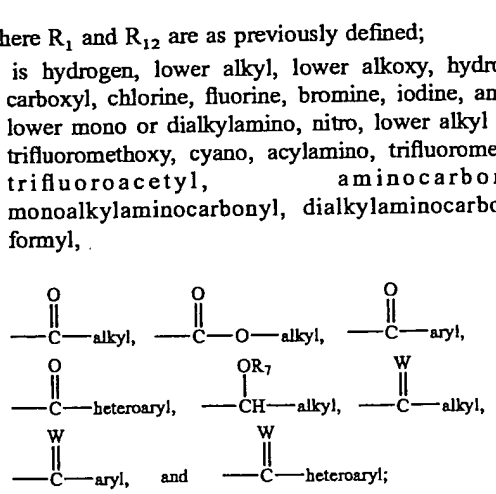


where $NR_{18}R_{19}$ taken together form a ring structure selected from the group consisting of piperidinyl, morpholinyl and piperazinyl;

—R_1—S—R_{12} (13)

where R_1 and R_{12} are as previously defined;

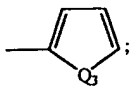
R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, formyl,



alkyl is lower alkyl;

aryl is as previously defined;

heteroaryl is



Q_3 is —O—, —S—,

—CH=N—;

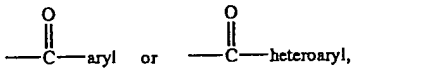
W is CH_2 or CHR_8 or N—R_9;

R_7 is hydrogen, lower alkyl, or acyl;

R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and

R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,



where aryl and heteroaryl are as defined above; and

m is 1, 2, or 3;

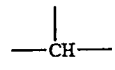
with the proviso that in formula (9) Z is not

when X is —S—, Q_2 is —CH_2—, Y is hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy, or trifluoromethyl, and p is 1 or 2;

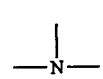
with the proviso that in formula (4) R_4 is not H when R_1 is R_{20}, Z is not

X is —S—S, Y is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or trifluoromethyl, and p is 1 or 2;

with the proviso that in formula (9) Z is not

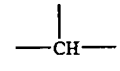


when X is



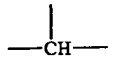
Y is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or trifluoromethyl and Q_2 is —CH_2—;

with the proviso that in formula (9) Z is not



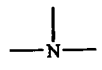
when X is —O—, Q_2 is —CH_2—, Y is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen, and p is 1 or 2;

with the proviso that in formula (9) Z is not

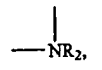


when X is —S—, Q_2 is —CH_2—, Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2, R is hydrogen, and m is 1;

with the proviso that in formula (9) Z is not

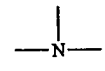


when X is



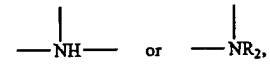
Q_2 is —CH_2—, R is chlorine, fluorine, bromine, iodine, lower alkyl, lower alkoxy, lower alkyl thio, lower mono- or dialkylamino, amino, cyano, hydroxy, trifluoromethyl; R_2 is aryl; Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2;

with the proviso that in formula (9) Z is not



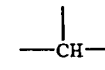
when

X is



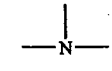
where R_2 is lower alkyl, aryl lower alkyl, or phenylsulfonyl, Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2 and Q_2 is —CH_2—;

with the proviso that Y_2 is not the moiety of formula (8) when Z is



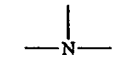
X is O, p is 1, and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

with the proviso that in formula (1) Z is not



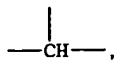
where X is O or S, Y is hydrogen, R is hydrogen, C_1–C_4 alkyl, chlorine, fluorine, bromine, iodine, cyano, C_1–C_4 alkoxy, aryl, —$COOR_{23}$ where R_{23} is C_1–C_4 alkyl;

with the proviso that in formula (1) Z is not



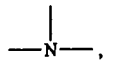
when X is —S—, R_1 is R_{20}, R is H, and m=1;

with the proviso that in formula (7) R_4 is not hydrogen when Y is 6-F, X is —O—, Z is

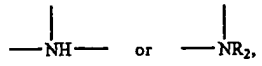


and n is 2, 3 or 4;

with the proviso that in formula (11) R_{12} is not H when Z is

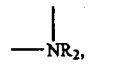


X is

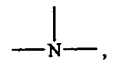


where R_2 is lower alkyl, aryl lower alkyl, or phenylsulfonyl Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group and p is 1 or 2;

with the proviso that in formula (11), R_{12} is not H when X is

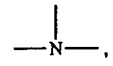


where R_2 is phenyl, Z is

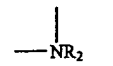


and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

with the proviso that in formula (12), R_{18} and R_{19} are not lower alkyl when Z is

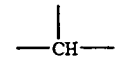


X is



R_2 is aryl and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

with the proviso that in formula (12), when X is —O—, Z is

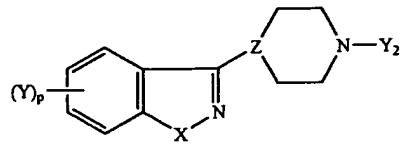


and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group, R_{18} and R_{19} are not lower alkyl;

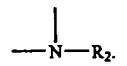
with the proviso that in formula (12), R_{18} and R_{19} are not hydrogen when R_1 is R_{20}, Z is —CH—, X is —O—, and Y is 6-F;

all geometric optical and stereoisomers thereof, or a pharmaceutically acceptable acid addition salt thereof.

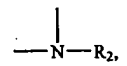
The compounds of the invention can also be represented by the following formula:



The substituent X in formula (I) is selected from the group consisting of —O—, —S—, —NH—, or



When the substituent X is —O—, the compounds of the invention contain a 1,2-benzisoxazole nucleus, and when X is —S—, the compounds of the invention contain a 1,2-benzisothiazole nucleus. When X is —NH— or

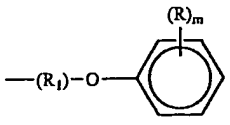


the compounds of the invention contain the indazole nucleus.

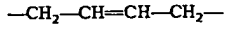
When p in formula (I) is 1, the substituent Y is selected from the group consisting of hydrogen, lower alkyl, hydroxyl, halogen, lower alkoxy, —CF_3, —NO_2, and —NH_2. The substituent Y is preferably in the 5- or 6-position of the ring. Moreover, in the preferred embodiments of the invention, the substituent Y is hydrogen, chlorine, bromine, or fluorine, and in the particularly preferred compounds of the invention. Y is fluorine, especially in the 6-position of the ring.

When p in formula (I) is 2 and X is —O—, each Y substituent can be independently selected from lower alkoxy, hydroxy or halogen groups, preferably methoxy groups.

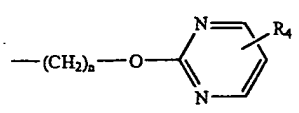
When the substituent Y_2 has the formula (b)(1):



and R_1 contains unsaturation, R_1 preferably has the formula

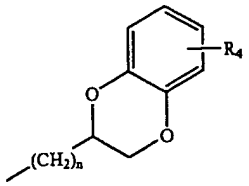


When the substituent Y_2 has the formula (b)(3):

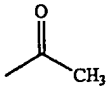


the substituent R_4 is preferably hydrogen or C_1–C_6 alkyl carbonyl and n is 3.

When the substituent Y_2 has the formula (b)(4):

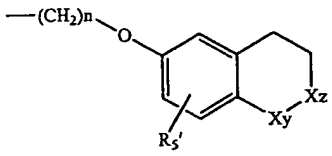


the substituent R_4 is preferably hydrogen or



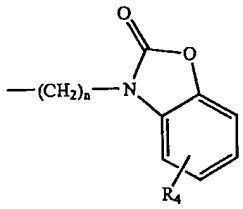
and n is preferably 1 or 2.

When the substituent Y_2 has the formula (b)(5):

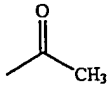


the substituent R_5' is preferably —OCH_3 and n is preferably 3.

When the substituent R_4 has the formula (b)(6):

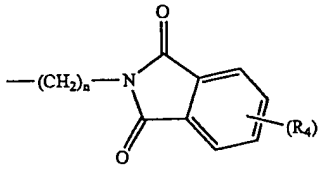


the substituent R_4 is preferably



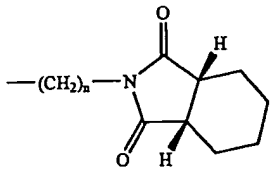
and n is preferably 3.

When the substituent Y_2 has the formula (b)(7):



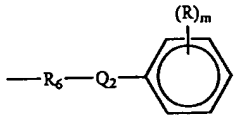
the substituent R_4 is preferably hydrogen and n is preferably 3 or 4.

When the substituent Y_2 has the formula (b)(8):



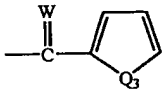
the value of n is preferably 3 or 4.

When the substituent Y_2 has the formula (b)(9):



the substituent R_6 is preferably —CH_2—CH=C—H—CH_2— when R_6 contains unsaturation.

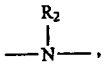
When the substituent R is



the substituent Q_3 is preferably —CH=N; and the substituent W is preferably CH_2, the substituent R_8 in CHR_8 is preferably CH_3, the substituent R_9 in N—R_9 is preferably hydroxy, lower alkoxy, or NH_2, and the substituent R_{10} in NHR_{10} is preferably hydrogen.

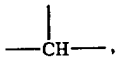
The value of n in the foregoing formulas can be 2, 3, 4, or 5, and preferably is 2, 3, or 4. In the particularly preferred compounds of the invention n is 3.

When X in the compounds of the invention is

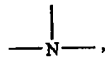


the substituent R_2 is selected from the group consisting of lower alkyl, aryl lower alkyl, aryl, cycloalkyl, aroyl, alkanoyl, and phenylsulfonyl groups.

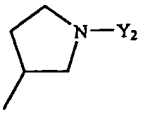
The substituent Z can be



in which case the compounds of the invention are heteroarylpiperidine derivatives, or



in which case the compounds are heteroarylpiperazine derivatives. When the substituent Q_1 has the formula



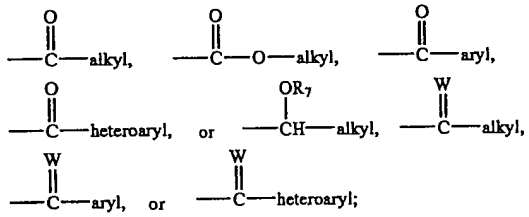
the compounds of the invention are heteroarylpyrrolidines.

The preferred compounds of the invention are the heteroarylpiperidines, i.e. compounds in which Z is

The compounds of the invention can contain one, two, or three R-substituents. The substituent R can be hydrogen, lower alkyl, C_1–C_6 alkoxy, hydroxyl, carboxyl, Cl, F, Br, I, amino, C_1–C_6 mono or dialkyl amino, —NO_2, lower alkyl thio, —OCF_3, cyano, acylamino, —CF_3, trifluoroacetyl (i.e.

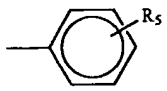
aminocarbonyl (i.e.

dialkylaminocarbonyl, formyl,

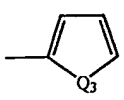


alkyl is lower alkyl;

aryl is phenyl or



where R_5 is hydrogen, lower alkyl, C_1–C_6 alkoxy, hydroxy, Cl, F, Br, I, C_1–C_6 alkylamino, —NO_2, —CN, —CF_3, —OCF_3; heteroaryl is



Q is —O—, —S—,

—CH=N—;

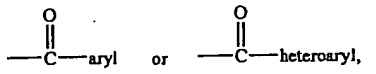
W is CH_2 or CHR_8 or N—R_9;

R_7 is hydrogen, lower alkyl, or acyl;

R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or —NHR10; and

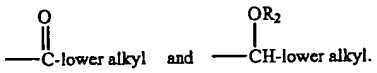
R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,



heteroaryl, where aryl and heteroaryl are as defined above; and

m is 1, 2, or 3.

When the compounds of the invention contain two or three R-substituents, each of the R-substituents can be independently selected from the above substituents. Preferably, each of the R-substituents is selected from the group consisting of hydrogen, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl, —$COCF_3$, C_1–C_6 alkanoyl, Cl, F, Br, I, C_1–C_3 alkylamino, —NO_2, —CF_3, —OCF_3,

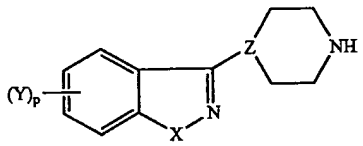


The compounds of the present invention are prepared in the following manner. The substituents R, R_1, R_2, R_3, X, Y, and Z and the integers m, n, and p are as defined above unless indicated otherwise.

B. PREPARATION OF COMPOUNDS OF THE INVENTION

The compounds of the invention can be prepared by reacting a piperidine or a piperazine of the formula:

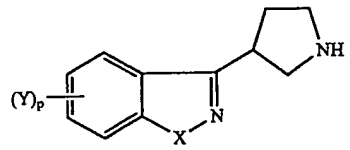
(3)



(1)

or a pyrrolidine of the formula:

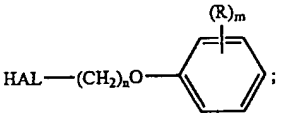
(3A)



(2)

under alkylating conditions with a compound of the formula:

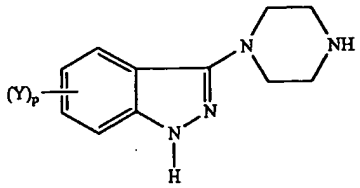
(4)



where HAL is Cl, Br, or I. The procedures that can be employed for preparing the piperidines, the piperazines, and the pyrrolidines and the alkylating agents identified by the above formulas will now be described in detail.

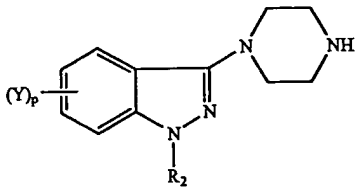
1. Preparation of 3-(1-unsubstituted-4-piperazinyl)-1H-indazoles

Compounds of the formulae:



and

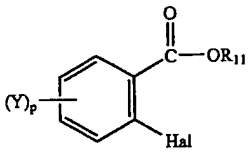
(6)



for use in synthesizing the indazolyl-substituted piperazines of the invention can be prepared as follows.

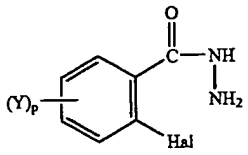
A substituted aryl ester of formula (7) is selected,

(7)



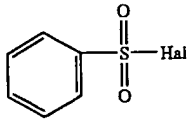
where R_{11} is lower alkyl and Hal is a halogen selected from the group consisting of Cl, Br, and I. The ester of formula (7) is reacted with hydrazine, H_2NNH_2, under standard hydrazide formation conditions. Typically, the reaction is carried out in a nonreactive solvent, e.g. ethanol, methanoL, or toluene, at a temperature of ambient temperature to the reflux temperature of the solvent for 4 to 16 hours to form a hydrazide of formula (8):

(8)



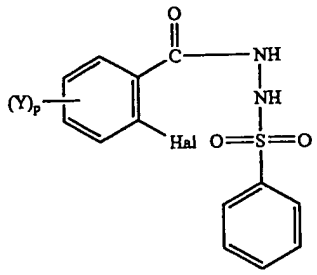
The hydrazide of formula (8) is reacted with a phenyl sulfonyl halide of the formula

(9)



where Hal is a halogen selected from the group consisting Cl and Br, to form a compound of the formula

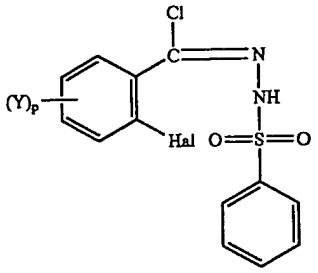
(10)



Typically this reaction is carried out in a basic solvent, such as pyridine or collidine, at a temperature of 0° to 30° C. for 2 to 16 hours.

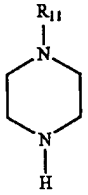
The compound of formula (10) in turn is reacted neat with thionyl chloride at a temperature of 50° to 79° C. (reflux temperature) for 2 to 16 hours to form a compound of formula (11)

(11)



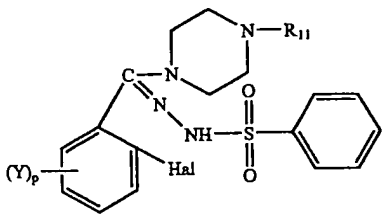
Compound (11) is reacted with a compound of formula (12),

(12)



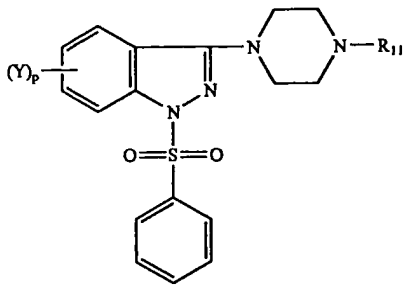
where R_{11} is lower alkyl, under conventional nucleophilic reaction conditions, for example in as font solvent, such as tetrahydrofuran (THF), toluene, or diethylether, at a temperature of 5° to 50° C. for 1to 16 hours to form a compound having the formula

(13)



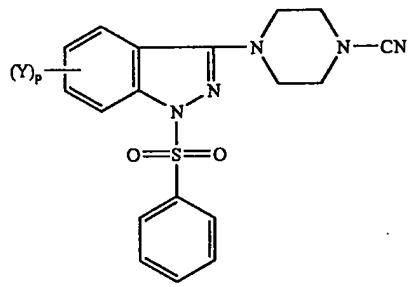
The compound of formula (13) is then reacted with a condensation agent, such a copper, copper-bronze, or cuprons oxide in a solved such as dimethylformamide dimethylacetamide, or tetramethylures, at a temperature of 120° to 177° C. for 1to 16 hours to form a piperazine-substituted phenylsulfonyl indazole of the formula

(14)



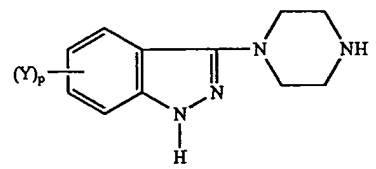
A cyano-substituted piperazine phenylsulfonyl indazole is then formed by reacting the compound of formula (14) with a conventional cyanation source, such as a halo-cyanide e.g. BrCN or ClCN, under conventional cyanation conditions, typically in an inert solvent e.g. dimethyl sulfoxide (DMSO) a $CHCl_3$ at ambient temperature for 2 to 16 hours to form a compound of formula

(15)



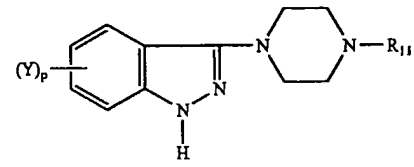
The compound of formula (5) is then subjected to reduction by means of a metal hydride, e.g. lithium aluminum hydride ($LiAlH_4$). Typically the reduction is carried out under standard reduction conditions in a solvent, such as tetrahydrofuran or diethyl ether, at a temperature of 33° to 67° C. for 6to 16 hours to forth a compound of formula (16).

(16)



A compound of formula (16) can be formed in an alternative manner by first reacting a compound of formula (14) with a strong base, much as a metal alcoholate, as sodium methoxide sodium ethoxide, or sodium butoxide, or with KOH in tetrahydrofuran to form a compound at formula (17);

(17)

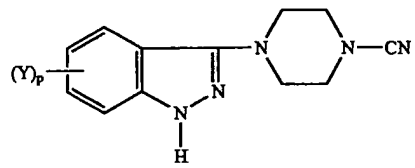


This reaction is typically carried as in a polar solvent, such as for example CH_3OH or C_2H_5OH, at a temperature of ambient to 50° C. for 1 to 16 hours.

Alternatively, the compound of formula (17) can be formed by reducing compound (14) with $LiAlH_4$ under conditions as previously described.

The compound of formula (17) in turn can be reacted with a cyanation reagent, as previously described, to form a cyano substituted piperazine indazole of the formula

(18)



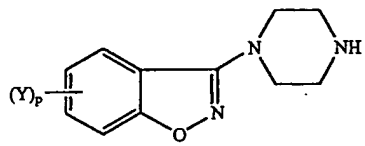
which in turn can be reduced with a metal hydride, as previously described, to form a compound of formula (16).

In an alternative embodiment, a compound of formula (18) can be reacted with an aqueous mineral acid, e.g. H_2SO_4 or HCl, at a temperature of 50° to 120° C. for 2to 16 hours to form a compound of formula (16).

2. Preparation of 3-(1-unsubstituted-4-piperazinyl)-1,2-benzisoxazoles

A compound of the formula:

(19)

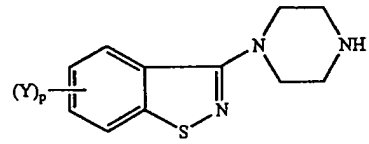


can be prepared according to conventional techniques. Suitable procedures are described in J. Med. Chem. 1986, 29:359. Compounds of formula (19) are useful for synthesizing the benzisoxazole substituted piperazines of the invention.

3. Preparation of 3-(1-unsubstituted-4-piperazinyl)-1,2-benzisothiazoles

A compound of the formula:

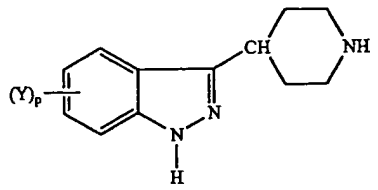
(20)



for use in synthesizing the benzisothiazole substituted piperazines of the invention can be prepared according to the techniques described J. Med. Chem. 1986, 29:359 and United Kingdom Patent (GB) 2 163 432 A.

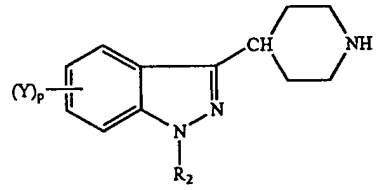
4. Preparation of 3-(1-unsubstituted-4-piperidinyl)-1H-indazoles

A compound of the formula:



(21)

or

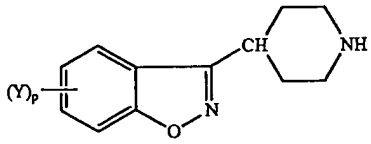


(22)

for use in synthesizing the piperidines of the invention can are be prepared using known techniques. For example suitable techniques are described in substantial detail i U.S. Pat. 4,710,573.

5. Preparation of 3-(1-unsubstituted-4-piperidinyl)-1,2-benzisoxazoles

A compound of the formula:

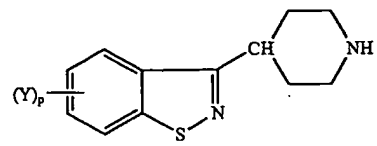


(23)

can be prepared by following the teachings from several sources. For example, U.S. Pat. No. 4,355,037 contains a detailed description of compounds of formula (23) and of methods for preparing the compounds. Additional disclosure of methods for preparing the compounds of formula (23) can be found in U.S. Pat. No. 4,327,103 and in Strupczewski et al., J. Med. Chem., 28:761–769 (1985). The compounds of formula (23) can be employed in the synthesis of the benzisoxazole substituted piperidines of the invention.

6. Preparation of 3-(1-unsubstituted-4-piperidinyl)-1,2-benzisothiazoles

Certain 3-(4-piperidinyl)-1,2-benzisothiazoles can be employed in the synthesis of the N-(aryloxyalkyl)-heteroaryl piperidines of the invention. Specifically, a benzisothiazole of the formula:

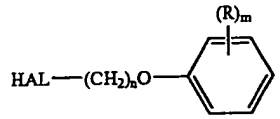


(24)

can be reacted with the alkylating agent previously described to form the N-(aryloxyalkyl)heteroarylpiperidines of the invention. Compounds of formula (24) and their methods of preparation are described in detail in U.S. Pat. No. 4,458,076.

7. Preparation of alkylating agents

The compounds described in Section 1-6 above can be reacted with alkylating agents of the formula:



(4)

to form the N-(aryloxyalkyl)heteroarylpiperidines, piperazines, and pyrrolidines of the invention. The alkylating agents of formula (4) and methods for preparing the alkylating agents are described in U.S. Pat. No. 4,366,162. Additional disclosure as be found in South African publication EA 86 14522. Is addition, procedures for making agents are described in the following Examples. These procedures can be employed to make other alkylating agents for use in this invention.

8. Alkylation of heteroarylpiperidines, piperazines, and pyrrolidines to form the compounds of the invention

The heteroarylpiperidines, piperazines, and pyrrolidines described in Sections 1–6 above can be reacted under alkylating condition with the alkylating agents described in Section 7to form the compounds of this invention. The reaction can be carried out by dissolving the reagents is an inert solvent, such as dimethylformamide, acetonitrile, or butanol, and allowing the reagents to react from a temperature of 50° C. to refluxing of the solvent in the presence of an acid receptor, such as a base. Examples of suitable bases are alkali metal carbonates, such as potassium carbonate, sodium carbonate, or sodium bicarbonate. The reaction can be carried out with or without a catalytic amount of an alkaline iodide, such a potassium iodide or sodium iodide, for a time sufficient to form a compound of formula (I) of the invention. Generally, the alkylation reaction is carried out for about 4to about 16 hours, depending on reactivity of the reagents. The reaction temperature can vary from about 50° to about 120° C. The products can be Isolated by treating the reaction product with water, extracting the product into in organic solvent that is immiscible in water, washing, drying, and concentrating the organic solvent to yield the free base, and then, if indicated, converting the resulting compound to an acid addition salt in a conventional manner.

Following are typical examples of compounds of the invention that can be prepared by following the techniques described above;

1-[4-[3-[4-(1H-indazol-3-yl)-1-piperanzinyl]propoxy]-3-methoxyphenyl]ethanone;

1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3methoxyphenyl]ethanone;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperanzinyl]propoxy]-3-methoxyphenyl]ethanone;

1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3methoxyphenyl]ethanone;

1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperandinyl]butoxy]-3-methoxyphenyl]ethanone;

1-[4-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone fumarate;

1-[4-[4-[4-(1H-indazol-3-yl)-1-piperanzinyl]butoxy]-3-methoxyphenyl]ethanone fumarate;

[4-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperandinyl] ethoxy]-3-methoxyphenyl]ethanone;

[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-2-piperandinyl] propoxy]-3-methoxy-α-methylbenzenemethanol;

[4-[3-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone;

[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperandinyl] propoxy]-3-hydrozyphenyl]ethanone;

[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperandinyl] propoxy]-3-methoxyphenyl]ethanone;

[4-[4-[4-(6-fluoro-1H-indazol-3-yl)-1-piperandinyl] butoxy]-3-methoxyphenyl]ethanone;

1-[4-[3-[4-(1H-indazol-3-yl)-1-piperanzinyl]propoxy]-3methoxyphenyl]ethanone;

1-[4-[3-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperandinyl]propoxy]-3-methoxyphenyl]ethanone;

1-[4-[4-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperandinyl]butoxy]-3-methoxyphenyl]ethanone fumarate;

[4-[3-[4-(5-fluoro-1,2-benzisoxazol-3-yl)-1-piperandinyl] propoxy]-3-methoxyphenyl]ethanone;

6fluoro-3-[1-[3-(2-methoxyphenoxy)propyl]-4-piperandinyl]-1,2-benzisoxazol fumarate;

[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperandinyl] propoxy]-3-methoxyphenyl]phenylmethanone;

1-[4-[4-[4-(1H-indazol-3-yl)-1-piperanzinyl]propoxy]-3-methoxyphenyl]ethanone;

1-[4-[2-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperandinyl]ethoxy]-3-methoxyphenyl]ethanone;

1-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperandinyl] propoxy]phenyl]ethanone fumarate;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperandinyl] propoxy]-2-methoxyphenyl]ethanone;

1-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperandinyl] propoxy]-5-methoxyphenyl]ethanone;

N-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]acetamide hemifumarate;

6-chloro-3-(1-piperazinyl)-1H-indazole;

1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl] propoxy]-2-methoxyphenyl]ethanone;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]ethanone hemifumarate;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]phenyl]ethanone;

1-[4-[3-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl] propoxy]-3-methoxyphenyl]ethanone;

1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone;

4-[3-[4-[(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxybenzonitrile;

1-[4-[4-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl] butoxy]-3-methoxyphenyl]ethanone;

1-[4-[3-[4-(6-benzoyl-6-fluoro-1H-indazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone sesquifumarate;

1-[4-[4-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]-butoxy]-3-methoxyphenyl]ethanone;

1-[4-[3-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-propoxy]-3-methoxyphenyl]ethanone hemifumarate;

1-[3,5-dibromo-4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperadinyl]-propoxy]phenyl]ethanone;

1-[4-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-ethoxy]-3-methoxyphenyl]ethanone;

6-fluoro-3-[1-(3-phenoxypropyl)-4-piperidinyl]-1,2-benzisoxazol;

1-[4-[2-[4-(6-chloro-1H-indazol-3-yl)-1-piperidinyl]-ethoxy]-3-methoxyphenyl]ethanone;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methylmercaptophenyl]ethanone;

1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperadinyl]butoxy]-3-methoxyphenyl]ethanone;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methylmercaptophenyl]phenylmethanone;

1-[3-bromo-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone;

3-[1-[3-[4-(1-ethoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole hydrochloride;

3-[1-3[-4-(1-acetoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole fumarate;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl) propoxy-3-methoxyphenyl]pentanone;

2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-N-methylbenzamine hemifumarate;

3-[1-[3-(4-bromo-2-methoxyphenoxy)propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]propanone;

4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzamide;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-(methylamino)phenyl]ethanone;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy[-3-ethoxyphenyl]ethanone;

N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]phenyl]acetamide;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-dimethylaminophenyl]ethanone;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-2-methoxyphenyl]ethanone hydrochloride;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]-2,2,2-trifluoroethanone;

4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxy-α-methylbenzenemethanol;

2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1piperidinyl]-propoxy]aniline dihydrochloride;

N-[5-acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)propoxy]phenyl]acetamide;

3-[1-[3-(4-ethyl-3methoxyphenoxy)propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole hydrochloride;

1-[3,5-dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl-1-piperidinyl]propoxy]phenyl]ethanone;

N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]phenyl]acetamide hemifumarate;

3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1piperidinyl]-propoxy]aniline;

3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1piperidinyl]-propoxy]-4-methoxyaniline;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1piperidinyl] propoxy-3methoxyphenyl]ethanone fumarate;

N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-4methoxyphenyl]acetamide;

1-[4-[3-(6-fluoro-1,2-benzisoxazol-3-yl)-1piperidinyl]-propoxy]-3methoxyphenyl]ethanone hydrochloride;

N,N-dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]ethanone oxime;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-methoxypenyl]ethanone oxime O-methyl ether;

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]ethanone hydrazone;

6-fluoro-3-[1-[3-[2-methoxy-4-(1-methylethenyl)-phenoxy] propyl]-4-piperidinyl]-1,2-benzisoxazole hydrochloride;

(Z)-1-[4-[(4-chloro-2-butenyl)oxy]-3-methoxyphenyl] ethanone;

(Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl]-ethanone;
(E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-hydroxyphenyl]ethanone hydrochloride;
(E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-benzyloxyphenyl] ethanone;
6-(3-chloropropoxy)-5-methoxy indole;
6-fluoro-3-[1-[3-[(5-methoxy-1H-indol-6-yl)oxy]-propyl]-4-piperidinyl]-1,2-benzisoxazole;
6-fluoro-3-[1-[3-[(1H-indol-7-yl)oxy]propyl]-4-piperidinyl] 01,2-benzisoxazole hemifumarate;
6-fluoro-3-[1-(3-hydroxypropyl]-4-piperidinyl]-1,2-benzisoxazole;
6-fluoro-3-[1-(2-pyrimidinoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate;
6-aceto-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan;
2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-methyl-1,4-benzodioxan;
2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl-1,4-benzodioxan;
6-(3-chloropropoxy)-7-methoxy-1-tetralone;
6-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-7-methoxy-1-tetralone;
N-(3-chloropropyl)-2-benzoxazolinone;
N-(3-chloropropyl)-6-acetyl-2-benzoxazolinone;
N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propyl-6-acetyl-2-benzoxazolinone;
N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propyl]phthalimide;
1-(3-aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidine dihydrochloride;
cis-2-(3-(4(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl) propyl-hexahydro-1H-isoindole-1,3-dione hydrochloride;
N-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-butyl]phthalimide;
1-(4-aminobutyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidine dihydrochloride;
cis-(2-(4-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-butyl)-hexahydro-1H-isoindole-1,3-dione hydrochloride;
1-[4-[[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propyl]thio]-3-methoxypheyl]ethanone;
4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2'-methoxyphenyl) butylpiperidine maleate;
4-(4-bromobutyl)-1-(1,2-dithian-2-yl)ethylbenzene;
1-[4-(1,3-dithian -2-yl)ethyl]phenyl-4-(6-fluoro-1,2-benzisoxazol-3-yl)butylpiperidine;
1-[4-(4'-acetophenyl)butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propylamino]-3-methoxyphenyl]ethanone;
(2,4-difluorophenyl)-[1-(phenylmethyl)-3-pyrrolidinyl]-methanone oxalate;
6-fluoro-3-[1-phenylmethyl)-3-pyrrolidinyl]-1,2-benzisoxazole fumarate;
(E)-1-[4-[(4-bromo-2-butenyl)oxy]-3-methoxyphenyl] ethanone;
4-(3-chloropropoxy)-3-methoxybenzaldehyde;
6-fluoro-3-(3-pyrrolidinyl)-1,2-benzisoxazole hydrochloride;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propylamino]-3-hydroxyphenyl]ethanone;
1-[3-acetylamino-4-(3-chloropropoxy)phenyl]ethanone;
N-[2-(3-hydroxypropoxy)phenyl]acetamide;
4-(3-chloropropoxy)-3-methoxybenzaldehyde;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methylpropoxy]-3-methoxyphenyl] ethanone;
(S)-(+)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methylpropoxy]-3-methoxyphenyl] ethanone;
(R)-(−)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methylpropoxy]-3-methoxyphenyl] ethanone;
1-[4-[3-[4-[(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2,2-dimethylpropoxy]-3-methoxyphenyl-]ethanone;
(±)-1-[1-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-phenylpropoxy]-3-methoxyphenyl] ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-(3-chlorophenyl) propoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-(phenylmethyl)propoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-1-methylpropoxy]-3-methoxyphenyl] ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methylpropoxy]-3-methoxyphenyl] ethanone;
(±)-1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methylbutoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-phenylbutoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-(2-phenylethyl)butoxy]-3-methoxyphenyl]ethanone;
(±)-[4-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-1-methylethoxy]-3-methoxyphenyl] ethanone;
(E)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-1-methyl-2-butenyl]oxy]-3-methoxyphenyl] ethanone;
(Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methyl-2-butenyl]oxy]3-methoxyphenyl] ethanone;
(±)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-1-propyl-2-butynyl]oxy]-3-methoxyphenyl] ethanone;
(S)-(+)-1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl]-2-methylpropoxy]-3-methoxyphenyl] ethanone;
(R)-(−)-1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl]-2-methylpropoxy]-3-methoxyphenyl] ethanone;
(±)-1-[4-[4-[4-(,2-benzisothiazol-3-yl)-1-piperidinyl]-3-methoxy]butoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-phenylpropoxy]-3-methoxyphenyl] ethanone; and
(±)-6-fluoro-3-[1-[3-(2-methyl-(2-methoxyphenoxy)-propyl]-4-piperidinyl]-1,2-benzisoxazole.

The compounds of the present invention are useful for treating psychoses by virtue of their ability to elicit a antipsychotic response in mammals. Antipsychotic activity is determined in the climbing mice assay by a method similar to those described by P. Protais, et al., Psychopharmacol., 50:1 (1976) and B. Costall, Eur. J. Pharmacol., 50:39 (1978).

Subject CK-1 male mice (23–27 grams) are group-housed under standard laboratory conditions. The mice are individu-

ally placed in wire mesh stick cages (4"×10") and are allowed one hour for adaption and exploration of the new environment. Then apomorphine is injected subcutaneously at 1.5 mg/kg a dose causing climbing in all subjects for 30 minutes. Compounds to be tested for antipsychotic activity are injected intraperitoneally or given oral doses at various time intervals, e.g. 30 minutes, 60 minutes, etc. prior to the apomorphine challenge at 8 screening doses of 10–60 mg/kg.

For evaluation of climbing, 3 readings are taken at 10. 20, and 30 minutes after apomorphine administration according to the following scale:

Climbing Behavior Mice with:	Score
4 paws on bottom (no climbing)	0
2 paws on the wall (rearing)	1
4 paws on the wall (full climb)	2

Mice consistently climbing before the injection of apomorphine are discarded.

With full-developed apomorphine climbing, the animals are hanging on to the cage walls, rather motionless, over long periods of time. By contrast, climbs due to mere motor stimulation usually only last a few seconds.

The climbing scores are individually totaled (maximal score: 6 per mouse over 3readings) and the total score of the control group (vehicle intraperitoneally-apomorphine subcutaneously) is set to 100%. ED_{50} values with 95% confidence limits, calculated by a linear regression analysis, of some of the compounds of the, present invention as well as a standard antipsychotic agent are presented in Table 1.

TABLE 1

COMPOUND	CLIMBING MOUSE ASSAY (ED_{50} mg/kg, ip)
1-[4-[3-[4-(1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone	0.98
1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone	0.67
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone	0.095
1-[4-[4-[4-(1,2-benzisoxazol-3-yl-1-piperidinyl]butoxy]-3-methoxyphenyl] ethanone	1.6
1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone	0.68
1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrochloride	0.16
2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,4-benzodioxan	0.29
(Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl]ethanone	0.61
1-[4-(4'-acetophenyl)butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine	0.34
6-fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole	4.1
4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl decanoate fumarate	3.31
1-(3-aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride	22.6

TABLE 1-continued

COMPOUND	CLIMBING MOUSE ASSAY (ED_{50} mg/kg, ip)
N-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]phthalimide	5.0
6-fluoro-3-[1-[3-[(isoquinol-5-yl)oxy] propyl]-4-piperidinyl]-1,2-benzisoxazole sesquifumarate	0.172
Chlorpromazine (standard)	1.3

Antipsychotic response, is achieved when the compounds of the present invention are administered to a subject requiring such treatment as an effective oral, parenteral, or intravenous dose of from 0.01 to 50 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the aforesaid compound. It is to be further understood that the dosages set forth herein are exemplary only and they do not, to any extent, limit the scope or practice of the invention.

Some of the compounds of the present invention are also useful as analgetics due so their ability to alleviate pain in mammals. The analgetic utility is demonstrated in the phenyl p-quinone writhing assay in mice, a standard assay for analgesia: Proc. Soc. Exptl. Biol. Med., 95:729 (1937). Thus, for instance the subcutaneous dose effecting an approximately 50% inhibition of writhing (ED_{50}) in mice produced in this assay is as shown in Table 2.

TABLE 2

COMPOUND	INHIBITION OF PHENYLQUINONE INDUCED WRITHING ED_{50} mg/kg, sc
1-[4-[3-[4-(1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone	0.06
1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone	0.17
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]ethanone	0.03
Propoxyphene (standard)	3.9
Pentazocine (standard)	1.3

Analgesia is achieved when the compounds of the present invention are administered to a subject requiring such treatment as an effective oral, parenteral, or intravenous dose of from 0.01 to 100 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the aforesaid compound. It is to be further understood that the damages set forth herein are exemplary only and that they do not, to any extent, limit the scope or practice of the invention.

Effective amounts of the compounds of the present invention can be administered to a subject by any one of several methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions.

The compounds of the present invention, while effective themselves, can be formulated and administered in the form

of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization, increased solubility, and the like. Preferred pharmaceutically acceptable addition salts include salts include salts of mineral acids, for example, hydrochloric acid, sulfuric acid, nitric acid, and the like; salts of monobasic carboxylic acids, for example, acetic acid, propionic acid, and the like; salts of dibasic carboxylic acids, for example, maleic acid, fumaric acid, and the like; and salts of tribasic carboxylic acids, such as carboxysuccinic acid, citric acid, and the like.

Effective quantities of the compounds of the invention can be administered orally for example, with an inert diluent or with an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purposes of oral therapeutic administration, compounds of the invention can be incorporated with an excipient and used in the form of tablets, troches, gums, and the like. These preparations should contain at least 0.5% of active compound of the invention, but can be varied depending upon the particular form and can conveniently be between 4% to about 70% of the weight of the unit. The amount of active compound in such a composition is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0–300 milligrams of the active compound of the invention.

Tablets, pills, capsules, troches, and the like can also contain the following ingredients: a binder, such as microcrystalline cellulose, gum tragacanth, or gelatin; an excipient, such as starch or lactose; a disintegrating agent such as alginic acid, primogel, corn starch, and the like; a glidant such as magnesium stearate or Sterores; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose; of saccharin, or a flavoring agent, such an peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms can contain various materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills can be coated with sugar, shellac, or other enteric coating agent. A syrup can contain in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes colorings, and flavors. Materials used preparing these various compositions should be pharmaceutically pure and non-toxic in the amount, used.

For the purpose of parenteral therapeutic administration, the active compound of the invention can be incorporated into a solution or suspension. These preparations should contain at least 0.1% a active compound, but can be varied between 0.5 and about 50% of the weight thereof. The amount of active compounds in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.5to 100 milligrams of active compound.

Solutions or suspensions can also include the following components: a sterile diluent, such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol, or other synthetic solvents; agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid, or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such at acetates, citrates, or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes, or multiple dose vials made of glass or plastic.

The following examples are for illustrative purposes only and are not to be construed as limiting the invention. All temperatures are given in degrees Centigrade (° C.) unless indicated otherwise.

EXAMPLE 1

Preparation of 1-[4-[3-[4-(1H-Indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone

(A) Synthesis of 3-bromobenzoic acid 2-phenylsulfonylhydrazide

To a solution of 2-bromobenzoic acid, hydrazide (132 g) in pyridine (1.2 l) cooled to about 10° with an ice bath, was added benzenesulfonyl chloride (7.3 ml). After complete addition, the reaction was stirred at ambient temperature for four hours, and then poured into ice-hydrochloric acid to precipitate a yellow solid, 135 g. The material was recrystallized from isopropanol to yield 125 g of 2-bromobenzoic acid 2-phenylsulfonylhydrazide, m.p.=154°–156° C.

(B) Synthesis of α-chloro-2-bromobenzaldehyde phenylsulfonylhydrazone

A mixture of 2-bromobenzoic acid phenylsulfonylhydrazide (125 g, (1.35 mol) and thionyl chloride (265 ml) was stirred and refluxed for 2hours. After about 15 minutes of reflux, the solid went into solution. The reaction was permitted to cool, and then it was poured into hexane. The resultant white solid was collected to afford 124 g of α-chloro-2-bromobenzaldehyde phenylsulfonylhydrazone, m.p.=120°–122° C.

(C) Synthesis of 1-[[(phenylsulfonyl)hydroaono]-2-bromophenyl)methyl]-4-methylpiperazine

To a stirred solution, under nitrogen, of α-chloro-2-bromobenzaldehyde phenylsulfonylhydrazone (271.1 g; 0.72 mol) in tetrahydrofuran (THF; 2liters), was added dropwise N-methylpiperazine (159.7 g; 1.6 mol). The reaction was stirred at ambient temperature for three hours, and then permitted to stand at ambient temperature for 16 hours. The reaction was chilled in an ice bath, and then filtered to remove the piperazine hydrochloride that was formed. The filtrate was concentrated to yield a brown gum. The gum was triturated with hot acetonitrile, the mixture was cooled in an ice bath, and when cold, was filtered to remove unwanted side product. The filtrate was then concentrated to afford 392.9 g of a brown gum of crude 1-[[(phenylsulfonyl) hydrazono]-(2-bromophenyrmethyl]-4-methylpiperazine.

(D) Synthesis of 3-(4-Methyl-1-piperazinyl)-1-phenylsulfonyl-1-indazole

A mixture of 1-[[(phenylsulfonyl)hydrazone]-(2-bromo phenyl)methyl]-4-methylpiperazine (31.0 g, 0.08 mol), copper bronze (3.1 g), K_2CO_3 (11.5 g), and dimethylformamide (500 ml), was stirred and refluxed for 1.5 hours. The reaction was poured into water and the aqueous suspension was stirred vigorously with ethyl acetate. The biphasic mixture was filtered through celite, and subsequently the layers were separated. The aqueous portion was extracted with another portion of ethyl acetate, and the combined extracts were washed (H_2O) and dried ($MgSO_4$). Concentration of the extract afforded a solid, which upon trituration with ether gave 19.7 g of solid. The solid was recrystallized from isopropanol afford 17.7 g (60%) of product, m.p. 158°–161° C. An analytical sample was obtained by another recrystallization from isopropanol (with charcoal treatment) to afford

colorless crystals of the indazole, 3-(4-methyl-1-piperazinyl)-1-phenylsulfonyl-1H-indazole, m.p.= 160°–161° C.

ANALYSIS

Calculated for $C_1H_{20}N_4O_2S$: 60.66% C 5.66% H 15.72% N.

Found: 60.45% C 5.62% H 15.61% N.

(E) Synthesis of 4-[1-(Phenylsulfonyl)-1H-indazol-3-yl]-1-piperazinecarbonitrile

To a stirred mixture of 3-(4-methyl-1-piperazinyl)-1-phenylsulfonyl-1H-indazole (237 g, 0.67 mol), K_2CO_3 (102 g, 0.74 mol) and dimethylsulfoxide (DMSO, 2000 ml), under nitrogen, was added cyanogen bromide (72 g, 0.68 mol) dissolved in DMSO (25 ml). The reaction was stirred at ambient temperature for 5.5 hours and was then poured into H_2O (7 l). The solid, which precipitated from solution, was collected by filtration, and was washed well with H_2O affording 168 g (68%) of product. A 5.2 g sample was recrystallized twice from ethanol-H_2O yielding 4.0 g of 4-[1-(phenylsulfonyl)-1H-indazol-3-yl]-1-piperazinecarbonitrile, m.p.=178°–180° C.

ANALYSIS

Calculated for $C_1H_{17}N_5O_2S$: 58.85% C 4.66% H 19.06% N.

Found: 59.01% C 4.63% H 19.09% N.

(F) Synthesis of 3-(1-Piperazinyl)]-1H-indazole

To a stirred mixture of 4-[1-(phenylsulfonyl)-1H-indazol-3-yl]1-piperazinecarbonitrile (163 g, 0.44 mol) in tetrahydrofuran (2.01) was added, dropwise, lithium aluminum hydride (880 ml, 0.88 mol of a 1M lithium aluminum hydride solution in tetrahydrofuran). After complete addition, the reaction was heated to reflux and stirred for 6hours, stirred at ambient temperature for one hour and allowed to sit at room temperature overnight. The reaction war quenched by the careful dropwise addition of water. After no more hydrogen could be observed to evolve, the reaction was filtered and the lithium salt filter cake was washed well with tetrahydrofuran. The filtrate was combined with the filtrate of another run (all together the starting material totaled 300 g, i.e. 0.82 mol) and the combined filtrates were concentrated to afford 372 g of a yellow solid suspended in water. An attempt was made to partition the product between water and dichloromethane, but the product proved to be only slightly soluble in dichloromethane. Therefore, the biphasic product suspension was filtered through a course sintered funnel and the white product which was collected was dried afford 121 g. The two phases of the filtrate were separated and the water was extracted again with dichloromethane. All of the dichloromethane phases were combined, washed twice with water, dried with magnesium sulfate, and concentrated to afford 41 g of a brown residue. The residue was triturated with diethyl ether and filtered to afford 10 g of a beige solid, m.p.=139°–150° C. The NMR and MS spectra were consistent with the structure. Recrystallization of 10 g from toluene afforded 7.3 g of 3-(1-piperazinyl)-1H-indazole, m.p.=153°–155° C.

(G) 3-4-Methyl-1-piperazinyl)-1H-indazole

A stirred mixture of 3-(-4methyl-1-piperazinyl)-1-phenylsulfonyl-1H-indazole (13.5 g, 0.038 mol), methanol (50 ml) and 25% CH_3ONa in methanol (15.3 ml) was stirred and refluxed for 2.5 h. The reaction was concentrated to about one-tenth its volume, and water was added to the mixture, resulting in a red solution. The solution was extracted with dichloromethane, the extract washed (H_2O), dried ($MgSO_4$), and the solvent was concentrated to afford 6.6 g of a rose-colored solid. Two recrystallizations from toluene-hexane afforded 4.3 g (52%) of 3-(4-methyl-1-piperazinyl)-1H-indazole as an off-white solid, m.p.= 111°–113° C.

ANALYSIS

Calculated for $C_{12}H_{16}N4$: 66.64% C 7.46% H 25–91% N.

Found: 66.83% C 7.42% H 25.69% N.

(H) 4-1H-indazol-3yl)-1-piperazinecarbonitrile

To a stirred mixture of cyanogen bromide (.3 g, 0.05 mol), K_2CO_3 (7.1 g) and dimethylsulfoxide (40ml) was added, dropwise, 3-(-4-methyl1-piperazinyl)-1H-indazole (11.0 g, 0.051 mol) dissolved in dimethylsulfoxide (60). The reaction was stirred at ambient temperature for 1 h, and then it was poured into water. The aqueous suspension was extracted with ethyl acetate, the ethyl acetate was washed (H_2O), dried ($MgSO_4$), and concentrated to afford 7.8 g (67%) of a yellow solid. This sample was combined with another and recrystallized twice from toluene to afford analytically pure 4-(1H-indazol-3-yl)-1-piperazinecarbonitrile as a white solid, m.p.=120°–122° C.

ANALYSIS

Calculated for $C_{12}H_{13}N_5$: 63.42% C 5.76% H.

Found: 63.04% C 5.84% H.

(I) Synthesis of 3-(1-Piperazinyl-1H-indazole

A mixture of 4 (1H-indazol-3-yl)-1-piperazinecarbonitrile (8.0 g, 0.04 mol) and 25% H_2SO_4 (100 ml) was stirred at reflux for 4.5 hours. The reaction was cooled in an ice bath and made basic by the dropwise addition of 50% NaOH. The basic solution was extracted with ethyl acetate. The ethyl acetate was washed with H_2O, dried with $MgSO_4$, and concentrated to afford 5.2 g (73%) of the desired compound, as a solid. The solid was recrystallized twice from toluene to afford 3.0 g of 3-(1-piperazinyl)-1H-indazole, m.p.= 153–158° C.

ANALYSIS

Calculated for $C_{11}H_{14}N_4$: 65.32% C 6.98% H 27.70% N.

Found: 65.21% C 6.99% H 27.70% N.

(J) Synthesis of 1-[4-[3-[4(1H-indazole-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(1-piperazinyl)-1H-indazole (4.0 g, 0.02 mol), K_2CO_3(3 g, 0.022 mol 1-[4-(3-chloropropoxy)-3-methoxypbenyl]ethanone (5.3 g, 0.022 mol), a few crystals of KI, and dimethylformamide (60 ml) was stirred at 90° C. for 5 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The extract was washed (brine), dried ($MgSO_4$), and the solvent was concentrated to afford a white solid, which was triturated with diethyl ether and collected to yield 7.0 g, of product. Two recrystallizatons from absolute ethyl alcohol yielded 5.3 g (64%) of analytically pure 1-[4-[3-(4-(1H-indazol-3-yl)-1-piperazinyl propoxy]-3-methoxyphenyl] ethanone, m.p.=155°–157° C.

ANALYSIS

Calculated for $C_{23}H_{28}N_8O_3$: 67.62% C 6.91% H 13.72% N.

Found: 67.45% C 6.74% H 13.56% N.

EXAMPLE 2

1-[4-[3-[4-(1,2-Benzisoxazol-3-yl)-1-piperadinyl] propoxyl]-3-methoxyphenyl]ethanone

A mixture of 3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (4.8 g, 0.02 mol), K_2CO_3 (5.2 g, 0.04 mol), 1-[4-

(3-chloropropoxy)-3-methoxyphenyl]ethanone (5.3 g, 0.022 mol), a few crystals of KI and dimethylformamide (60 ml) was stirred at 90° C. for 16 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$) and concentrated to afford a brown oil. The oil was chromatographed on a Waters Prep 500 utilizing silica gel columns and ethyl acetatediethylamine (2%), eluent. Concentration of the appropriate fractions afforded 3.9 g of product as an off-white solid. Recrystallization from absolute ethyl alcohol afforded 26 g (33%) of 1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-phenyl]ethanone, m.p.=102°101° C., as colorless needles.

ANALYSIS

Calculated for $C_{24}H_{28}N_2O_4$: 70.56% C 6.91% H 6.86% N.

Found: 70.73% C 6.93% H 6.85% N.

EXAMPLE 3

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperadinyl]propoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (5.1 g, 0.02 mol), K_2CO_3 (5.2 g. 0.04 g, mol), 1-(4-(3-chloropropoxy-3-methoxyphenyl] ethanone (5.3 g, 0.022 mol), and dimethylformamide (60 ml) was heated at 90° C. for 16 hour. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$) and concentrated to afford a moist solid. Recrystallization (twice) from ethyl alcohol afforded 5.0 (58%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3methoxyphenyl]ethanone as a beige solid, m.p.=118°–120° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_4$: 67.60% C 6.38% H 6.57% N.

Found: 67.47% C 6.40% H 6.53% N.

EXAMPLE 4

1-[4-[4-[4-(1,2-Benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanol

A mixture of 3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (4.3 g, 0.018 mol), K_2CO_3 (5.5 g, 0.04 mol), and 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (5.5 g, 0.018 mol), and dimethylformamide (60 ml) was stirred and heated at 75° C. for 16 hours. The reaction was poured into water and was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and the solvent concentrated to afford 7.2 g of a beige solid. Recrystallization (twice) from ethyl alcohol yielded 3.3 g (43%) of 1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]3-methoxyphenyl]ethanone, m.p.=99°–101° C.

ANALYSIS

Calculated for $C_{25}H_{30}N_2O_4$: 71.11% C 7.16% H 6.63% N.

Found: 70.76% C 7.24% H 6.58% N.

EXAMPLE 5

1-[4-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)butoxy]-3-methoxyohenylethanone

A stirred mixture of 6-fluoro-3-piperidinyl)-1,2-benzisoxazole hydrochloride (5.1 g, 0.02 mol), K_2CO_3 (5.2 g, 0.04 mol), 1-(4-(4-bromobutoxy)-3-methoxyphenyl] ethanone (6.6 g, 0.022 mol), and dimethylformamide (60 ml) was heated at 75° C. for 5 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and the solvent was concentrated to yield initially an oil, which solidified upon standing. The solid was triturated with hexane and collected to afford 7.7 g of the product as a waxy solid. The compound was chromatographed on a Waters Prep 300 utilizing silica gel columns and eluting with dichloromethane/methanol (5%). Concentration of the appropriate fractions yielded 5.1 g of off-white solid 1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone, which when recrystallized from ethyl alcohol yielded 3.2 g (36%) of feathery-white needles, m.p.=88°–90° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_4$: 68.16% C 6.64% H 6.36% N. Found: 6796% C 6.49% H 6.29% N.

EXAMPLE 6

1-[4-[2-[4-(1,2-Benzisoxazole-3-yl)-1-piperidinyl] ethoxy]-3-methoxyphenyl]ethanone fumarate

A mixture of 3-(-4-piperidinyl)-1,2-benzisoxazole hydride (4.8 g, 0.02 mol), K_2CO_3 (5.2 g, 0.04 mol), 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone (5.0 g, 0.022 mol), and dimethylformamide (90 ml) was heated at 90° C. for 16 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_3$), and the solvent was concentrated to afford an oil. Upon standing, the oil solidified to afford a beige solid. The crude solid was recrystallized twice from ethyl alcohol to afford 3.9 g of an off-white solid. The solid was dissolved is ethyl acetate, and fumaric acid (.2 g. 1.1 equiv.) was added. The mixture was heated briefly on a steam bath, and then stirred at ambient temperature for 2hours. An initial green oil settled out and the supernatant solutions was decanted. Ether was added to the decantate and 4.0 g of a white fumarate salt was collected. The salt was recrystallized twice from ethanol-ether to yield 1.7 g (17%) of 1-[4-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone fumarate, m.p.=127°–129° C.

ANALYSIS

Calculated for $C_{23}H_{26}N_2O_4C_4H_4O_4$: 63.52% C 5.92% H 5.49% N.

Found: 63.00% C 5.87% H 5.42% N.

EXAMPLE 7

1-[4-[4-[4-(1H-indazol-3-yl)-1-piperizinyl]butoxy]-3-methoxyphenyl]ethanone fumarate

A stirred mixture of 3-(1-piperazinyl)-1H-indazole (4.0 g, 0.02 mol). K_2CO_3 (5.3 g, 0.04 mol), 1-[4-(4-bromobutoxy)-3methoxyphenyl]ethanone (6.6 g, 0.022 mol), and dimethylformamide (60 ml) was heated at 75° C. for 6hours. The reaction was poured into water, and a white solid precipitated from solution. The solid was collected and dried to afford 7.2 g of the crude product. The crude solid was recrystallized twice from ethyl alcohol to yield 4.1 g of the free base, which was converted to its fumarate salt by the addition of fumaric acid (1.1 g) to the compound dissolved in refluxing acetone. The resulting fumarate salt (5.0 g) was recrystallized from ethyl alcohol to afford 3.8 g (35%) of 1-[4-[4-[4-(1H-indazol-3-yl)-1-piperizinyl]butoxy)-3-methoxy phenyl]ethanone fumarate, as a white solid, m.p.= 163°–165° C.

ANALYSIS

Calculated for $C_{24}H_{30}N_4O_3.C_4H_4O_4$: 62.44% C 6.36% H 10.40% N. Found: 62.28% C 6.62% H 10.34% N.

EXAMPLE 8

1-[4-[2-[4-(-6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2 benzisoxazole hydrochloride (5.1 g, 0.02 mol), K_2CO_3 (5.2), 1-[4-(2-chloroethoxy)-3-methoxypbenyl]ethanone (5.0 g, 1.022 mol), and dimethylformamide (90 ml) was heated at 90° C. For 16 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and concentrated to afford 7.4 g of a yellow solid. The solid was chromatographed on a Waters Prep LC 500 utilizing dichloromethane/methanol (4%) as eluent, and subsequent concentration of the appropriate fraction afforded 4.0 g of a yellow solid. The solid was recrystallized from ethyl alcohol to yield 3.1 g (38%) of 1-[4-[2-[4-(-6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone, as slightly yellow flakes m.p.=132°–134° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_4$: 66.98% C 6.11% H 6.79% N.

Found: 66.90% C 6.20% H 6.74% N

EXAMPLE 9

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxy-α-methylbenzenemethanol

To a stirred mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-3-yl)-1-piperidinyl]propoxy-3-methoxyphenyl]ethanone (4.0 g 0.0094 mol) in methanol/tetrahydrofuran (60ml, 1:1), was added sodium borohydride (0.4 g, 0.01 mol). After an initial evolution of gas, all insolubles went into solution. The reaction was stirred at ambient temperature for 3hours and TLC at this time showed a very slight amount of starting ketone. Therefore, another 0.1 g of sodium borohydride was added, and stirring was continued for an additional 0.5 hour. TLC now showed complete disappearance of starting material The reaction was concentrated to an off white residue, which was diluted with water and collected to yield 3.4 g of alcohol. This was recrystallized from toluene (twice, with a charcoal treatment) to yield 2.7 g (67%) of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methoxy-α-methylbenzene-methanol as a white solid, m.p.=136°–138° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_2O_4$: 67.27% C 6.82% H 6.45% N.

Found: 67.59% C 6.89% H 6.47% N.

EXAMPLE 10

1-[4-[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(4-piperidinyl)-1,2-benzisothiazole (3.0 g. 0.0137 mol), potassium carbonate (2.3 g, 0.0165 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (4.0 g, 0.0165 mol), potassium iodide (200 mg) and acetonitrile (100 ml) was stirred at reflux under N_2 for 24 hours. The cooled reaction was filtered and the cake was washed well with acetonitrile. The filtrate was concentrated to an oily residue, which was partitioned between water and ethyl acetate. The ethyl acetate extract was washed well with water, dried with $MgSO_4$ and concentrated to yield 6.1 g of a beige oil upon solidified on standing. The product was triturated with diethyl ether and filtered to give 42 g of a beige solid. The compound was recrystallized from ethyl alcohol to afford 3.5 g, and another recrystallization from ethyl alcohol (utilizing decolorizing carbon) provided 2.4 g (41%) of 1-[4-[3-[4-(1,2 benzisothiazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]ethanone, m.p.=93°–96° C.

ANALYSIS

Calculated for $C_{24}H_{28}N_2O_3S$: 67.90% C 6.65% H 6.60% N.

Found: 67.89% C 6.61% H 6.39% N.

EXAMPLE 11

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperdinynl]propoxy]-3-hydroxyphenyl]ethanone

(A) Synthesis of 1-[4-(3-hydroxyphenyl]ethanone

To a stirred solution of 1-[4-(3-chloropropoxy)-3 methoxyphenyl]ethanone (10.0 g, 0.041 mol) in methylene chloride (120 ml) cooled to −50° C. (dry ice-methanol) was added, dropwise, 1M boron tribromide in methylene chloride (123 ml, 0.12 mol). The temperature was kept between −40° C. and −50° C. After compete addition, the reaction was permitted to reach −30° C., and the TLC checked (ca. 15 min. after final boron tribromide was added). Saturated $NaHCO_3$ was added, dropwise, never allowing the temperature to go above 0° C. during most of the addition. When sufficient $NaHCO_3$ had been added to make the solution basic, the organic layer was collected. The layer was washed with brine, dried ($MgSO_4$), and concentrated to yield 8.1 g of dark brown oil, which solidified on standing. This was chromatographed an a Waters Prop 500 LC (2silica columns, 2% methanol methylene chloride as eluent). Upon concentration of the appropriate factions, 5.8 g of a brown tacky solid were obtained. This was recrystallized from isopropyl other (with decanting of the yellow isopropyl ether supernatant from the dark brown oily residue) to give initially 2.5 g of a yellow solid. Concentration off the mother liquor gave as additional 0.5 g, m.p.=110°–113° C.

(B) Synthesis of 1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3hydroxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.8g, 0.013 mol) $NaHCO_3$ (1.1 g), several crystal of KI, 1-[4-(3-chloropropoxy)-3-hydroxyphenyl] ethanone, and acetonitrile (100 ml) was refluxed for 16 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The organic extract was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford 5.7 g of a thick yellow oil. The oil was chromatographed on a Waters Prep 500 LC on silica gel, eluting with 7% methanol/methylene chloride. Concentration of the appropriate fraction afforded a yellow oil, which upon standing yielded 3.5 g of the compound as a pale, yellow solid. The solid was recrystallized from ethyl alcohol to afford 2.7 g (50%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazole-3-yl)-1-piperidinyl[propoxy]-3-hydroxyphenyl]ethanone as a pale Yellow solid, m.p.= 122°–124° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_4$: 66.98% C 6.11% H 6.79% N.

Found: 66.97% C 6.20% H 6.69% N.

EXAMPLE 12

1-[4-[3-[4-(6-Fluoro-1H-indazol-3-yl)-1-piperazinyl]-propoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(1-piperazinyl)-1H-indazole (2.3 g, 0.01 mol), K_2CO_3(1.5 g), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (2.8 g, 0,011 mol), several crystals of KI and dimethylformamide (60ml) was heated at 90° C. for 16 hours. The reaction was poured into H_2O, and the aqueous suspension was extracted with ethyl acetate. The ethyl acetate was washed (H_2O), dried ($MgSO_4$) and concentrated to afford 5.0 g of a yellow oil. The oil was chromatographed on a Waters Prep 500 utilizing silica gel columns and eluting with methylene chloride/methanol (7%). Concentration of the desired fractions yielded 2.0 g (46%) of an off-white solid. This sample was combined with 1.0 g of a previous sample, and this was recrystallized from toluene to afford 2.6 g of 1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl)ethanone as a white solid, m.p.=135°–137° C.

ANALYSIS

Calculated for $C_{23}H_{27}FN_4O_3$: 64.77% C 6.38% H 13.14% N.

Found: 64.66% C 6.21% H 13.02% N.

EXAMPLE 13

1-[4-[4-[4-(6-Fluoro-1H-indazol-1-piperazinyl]-butoxy]-3-methoxyphenyl)ethanone

A stirred mixture of 6-fluoro-3-(-1-piperazinyl)-1H-indazole hydrochloride (5.0 g, 0.019 ml), K_2CO_3 (5.8 g) and 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (6.3g, 0.021 mol) and dimethylformamide (80ml) was heated at 73° C. for 6hours. The reaction was poured into water and an off-white solid formed from solution. The solid was collected and dried to yield 4.5 g of crude product. The compound was recrystallized from ethanol (3times) to afford 3.0 g of an off-white solid. The solid was chromatographed on a Waters Prep 500 utilizing silica gel columns and eluting with methylene chloride/methanol (7%). Concentration of the appropriate fractions afford 2.3 g of an off-white solid, which when recrystallized from ethanol yielded 1.9 g (26%) of analytically pure 1-[4-[4-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone, m.p.= 156°–138° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_4O_3$: 63.44% C 65.44% H 12.72% N.

Found: 65.38% C 6.49% H 12.60% N.

EXAMPLE 14

1-[4-[3-[4-(1H-Indazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(-4-piperidinyl)-1H-indazole (3.0 g, 0.015 mol), K_2CO_3 (1.6), 1-]4-(-3-chloropropoxy)-3-methoxyphenyl]ethanone (5.3 g; 0.022 mol), a few crystals or KI and acetonitrile (100 ml) was stirred and refluxed for 16 hours. The reaction was poured into water and a white solid separated from solution. The solid was collected, dried and afforded 5.1 g of product. Recrystallization from ethanol yielded 3.6 g of the compound, which upon chromatography (preparative HPLC on silica gel, eluting with methylene chloride/-methanol-9:1) gave 3.0 g (49%) of an off-white solid. Recrystallization from ethanol afforded the analytically pure 1[4-[3-[4-(1H-indazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]ethanone as a white solid, m.p.=171°–173° C.

ANALYSIS

Calculated for $C_{24}H_{29}N_3O_3$: 70.74% C 7.17% H 10.31% N. Found: 70.52% C 7.27% H 10.42% N.

EXAMPLE 15

1-[4-[3-[4-(6-Chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-methoxyphenyl]ethanone

A stirred mixture of 6-chloro-3-(4-piperidinyl)-1,2-benzisoxazole (4.7 g, 0.02 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl] ethanone (4.8 g, 0.02 mol, K_2CO_3 (2.8), several crystals of KI and acetonitrile (120 ml) was refluxed for 16 hours. The reaction was filtered and the filtrate was concentrated to yield a solid-oil mixture. The residue was chromatographed on a Waters Prep 500 utilizing silica columns and eluting with methylene chloride/methanol (5%). Concentration of the desired fractions yielded 3.2 g of a beige solid, which upon recrystallization from ethanol afforded 2.7 (31%) of 1-[4-[3-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperdinyl]propoxy]-3-methoxyphenyl]ethanone as a beige solid, m.p.=116°–118° C.

ANALYSIS

Calculated for $C_{24}H_{27}ClN_2O_4$: 65.08% C 6.14% H 6.32% N.

Found: 65.35% C 6.22% H 6.28% N

EXAMPLE 16

1-[4-[4-[4-(6-Chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone fumarate

A stirred mixture of 6-chloro-3-(4-piperidinyl-1,2-benzisoxazole (4.7 g, 0.02 mol), 1-[4-[4(4-bromobutoxy)-3methoxyphenyl]ethanone (6.0 g, 0.02 mol), K_2CO_3(2.8) and acetonitrile (120 ml) was refluxed for 16 hours. The reaction was allowed to cool, filtered, and the filtrate was concentrated to 9.9 g of a brown oil. The oil was chromatographed on a Waters Prep 500 utilizing silica gel columns and eluting with methylene chloride/methanol (5%). Concentration of the appropriate fractions afforded 2.3 g of an off-white solid. The solid was dissolved in ethanol and fumaric acid (0.62 g, 1.1 eq) was added. Upon concentration of the ethanol, a crude, brown solid was collected, which was taken up in refluxing acetone. Upon cooling a white solid crystallized from solution yielding 2.2 g (19%) of 1-[4-[4-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl] butoxy]-3-methoxyphenyl]ethanone fumarate as a white solid, m.p.=139°–141° C.

ANALYSIS

Calculated for $C_{25}H_{29}ClN_2O_4$: $C_4H_4O_4$: 60.78% C 5.80% H 4.89% N.

Found: 60.69% C 5.74% H 4.85% N.

EXAMPLE 17

1-[4-[3-[4-(5-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone

A mixture of 5-fluoro-3-(-4-piperidinyl)-1, 2benzisoxazole (2.2 g, 0.01 mole), 1-[4-(3-chloropropoxy)-

3-methoxyphenyl]ethanone (24g, 0.01 mole), K_2CO_3 (1.4 g), a few crystals of KI and acetonitrile (100 ml) was stirred and refluxed for 8hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate . The ethyl acetate extract was washed (brine), dried ($MgSO_4$) and concentrated to afford 4.0 g of a white solid. The solid was chromatographed on a Waters Prep 500 HPLC utilizing silica gel columns and eluting with methylene chloride/ methanol (5%). Concentration of the appropriate fractions afforded 2.0 g (47%) of 1-[4-[3-[4-(5-fluoro-1,2-benzisoxazol-[3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone as a white crystalline solid, m.p.= 103°–105° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O$: 67,59% C 6.38% H 6.57% N.

Found with): 67.50% C 6.47% H 6.53% H.

EXAMPLE 18

6-Fluoro-3-[1-[3-(-2-methoxyphenoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate

A stirred mixture of 6-fluoro-3-(-4-piperidinyl)-1,2-benzisoxazole (2.45 g; 11.1 mmoles), K_2CO_3 (2.0) and 3-(2-methoxyphenoxy)propyl chloride (3.5 g, 17.4 moles) is acetonitrile (40ml) was heated at 90° C. for 4hr. At the and of the reaction, the advent was removed, and the solids were dissolved into dichloromethane (100 ml). The solution was washed with water and brine, then dried over $MgSO_4$. The craft material from the solution was combined with 1.2 g of crude material, prepared in the same fashion (using 0.5 g of starting material). The combined material was purified by flash chromatography on a silica gel column (49g, eluted with 0.5% diethylamine: 1% methanol: 98.5% dichloromethane, 1 l). The fractions containing the pure product were pooled and concentrated down to a light oil (3.68). This oil was treated with fumaric acid (1.14 g, 9.8 mmoles) in ethanol (13ml). The 6-fluoro-3-[1-[3-(2-methoxyphenoxy)propyl]-4piperidinyl]1.2-benzisoxazole fumarate crystals obtained weighed 4.01 g (60%), m.p.= 169°–170° C.

ANALYSIS

Calculated for $C_{22}H_{25}FN_2O_3.C_4H_4O_4$: 62.39% C 5.84% H 5.60% N.

Found: 62.37% C 5.88% H 5.60% N.

EXAMPLE 19

1-[3-[3-[4-(-6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl] phenylmethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2 benzisoxazole (2.01 g; 9.13 moles), K_2CO_3 (2.0 g), and 1-[3-(3-chloropropoxy)-4-methoxyphenyl]phenylmethanone (3.93 g; 11.3 moles) and acetonitrile (50ml) was heated at reflex for 4hr. At the and of the reaction, the solvent was evaporated and the residue was partitioned between water (150 ml) and dichloromethane (400 ml). The dichloromethane solution was washed with water and brine (100 ml), dried over $MgSO_4$, then concentrated to an oil. The purification was done by flash chromatography over a silica gel column (SiO_2, 40 g; eluted with dichloromethane, 300 ml; 1% methanol in dichloromethane, 850 ml). The material thus obtained as a colorless oil solidified on standing. Recrystallization from ethanol (150 ml) gave 1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]phenylmethanone as white crystals, 3.07 g (63%, m.p.=140°–141° C.

ANALYSIS

Calculated for $C_{29}H_{29}FN_2O4$: 71.30% C 5.98% H 5.73% N.

Found: 71.09% C 5.98% H 5.73% N.

EXAMPLE 20

1-[4-[4-[4(1H-indazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(4-piperidinyl)-1H indazole (3.2 g, 0.016 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (5.0 g, 0.016 mol) K_2CO_3 (2.2) and acetonitrile (100 ml) was stirred and refluxed for 6hours. The reaction was poured into water and the resulting yellow solid that formed was collected to afford 5.3 g of product. The compound was recrystallized from acetonitrile and then from ethyl acetate to yield 3.0 g (45%) of a slightly yellow solid of 1-[4-[4-[4-(1H-indazol-3-yl)-1-piperidiyl]butoxy]-3-methoxyphenyl]ethanone, m.p.=133°–135° C.

ANALYSIS

Calculated for $C_{25}H_{31}N_3O3$: 71.23% C 7.41% H 9.97% N.

Found: 70.85% C 7.61% H 9.81% N.

EXAMPLE 21

1-[4-[2-[4-(6-Chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3methoxyphenyl]ethanone

A stirred mixture of 6-chloro-3-(4-piperidinyl)-1,2 benzisoxazole (4.6 g. 0.019 mol) 1-[4-(2-chloroethoxy)-3methoxyphenyl]ethanone (4.3 g. 0.019 mol), K_2CO_3 (2.8), a few crystals of KI and acetonitrile (120 ml) was refluxed for 16 hours. The reaction was filtered and the filtrate was concentrated to yield 8.0 g of yellow solid. The solid was chromatographed on a Waters Prep 500 LC (silica columns, eluting with methylene chloride/-methanol, 5%). Concentration of the appropriate fractions yielded 3.2 g of a light yellow solid, which upon recrystallization from ethyl acetate afforded 2.3 g (28%) of 1-[4-[2-[4-(6-chloro-1.2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone as a pale yellow solid, m.p.= 133°–135° C.

ANALYSIS

Calculated for $C_{23}H_{25}ClN_2O4$: 64.41% C 5.88% H 6.33% N.

Found: 64.351% C 5.87% H 6.41% N

EXAMPLE 22

3-(3-Bromopropoxy-4-methoxyphenyl) phenylmethanone

A solution of 3-hydroxy-4-methoxybenzophenone (4.6 g, 20 mmoles) in dimethylformamide (35ml) was treated with sodium hydride (600 mg, 25 mmoles) at 0° C. for 20 minutes, then 1,3-dibromopropane (5g, 24.7 moles was added in one portion. The mixture was heated at 90° C. for 1hr, and then stirred at room temperature for 2hr. At the end of the reaction, the mixture was poured into water (500 ml) and extracted with ethyl acetate (400 ml). The ethyl acetate solution was washed with water, brine and dried over anhydrous $MgSO_4$. The solvent was removed and the crude oil was purified by flash chromatography over a silica gel column (SiO_2, 85 g; eluted with 3l hexane:dichloromethane, 1.6; 3:7 hexane:dichloromethane, 1.41). The pure product thus obtained weighed 4.67 g, (66%) as an oil. Recrystallization twice from isopropyl ether (500 ml) gave analytically

pure 3-(3-bromopropoxy-4methoxyphenyl)-phenylmethanone (2.42 g). m.p.=81°–83° C.

ANALYSIS

Calculated for $C_{17}H_{17}BrO_3$: 58.47% C 4.91% H

Found: 58.63% C 4.82% H.

EXAMPLE 23

1-[3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone fumarate

A mixture of 6-fluoro-3-(-4-piperidinyl)-1.2-benzisoxazole hydrochloride (4.53 in, 20.5 moles), K_2CO_3 (4.5 m), 1-[3-(3-chloropropoxy)phenyl]ethanone (6.4 g. 29 moles) in acetonitrile (60ml) was heated at reflux for 5hr. At the end of the reaction, the solvent was removed and the residue was extracted into dichloromethane (300 ml). The inorganic insolubles were filtered off. The dichloromethane solution was concentrated to a small volume (10 ml) and purified on a flash chromatographic column (SiO_2. 75 g, eluted with dichloromethane, 900 ml; and 2% methanol in dichloromethane, 800 ml). The fractions containing the pure product were combined and concentrated to an oil (2.87 g, 35%). The oil was dissolved into ethanol and treated with a solution of fumaric acid (841 mg). Recrystallization (twice) from ethanol afforded 2.53 g of 1-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl)ethanone fumarate as white crystals, m.p.=172°–174° C.

ANALYSIS

Calculated for $C_{22}H_{25}FN_2O_3.C_4H_4O_4$63.27% C 5.70% H 5.47% N.

Found: 63.04% C 5.63% H 5.43% N.

EXAMPLE 24

1-[4-[3-[-4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-methyphenyl]ethanone

A stirred mature of 6-fluoro-3-(-4-piperidinyl)-1,2 benzisoxazole hydrochloride (5.5 g, 21.6 mmoles), K_2CO_3 (3.6 gm), 1-[4-(3-bromopropoxy)-2-methylphenyl]ethanone (4.83 g, 17.8 mmoles),in dimethylformamide (25ml) and acetonitrile (75ml) was heated at 120° C. for 5 hr. At the and of the reaction, the solvent was removed and the residue was extracted into dichloromethane (300 ml) and the solution was washed with water and brine. The organic solution was dried and evaporated to a crude oil. The purification was done by flash chromatography over a silica gel column (80g, eluted with dichloromethane, 1 l; 1% methanol:dichloromethane, 1.2 l; 2% methanol:dichloromethane, 1.2 l). The purest fractions were combined and afforded 2.91 g of solid. Recrystallization from dichloromethane and ethanol gave 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2methylphenyl]ethanone as off-white crystals: 2.42 g, m.p.= 113°–114° C.

Calculated for $C_{24}H_{27}FN_2O3$: 70.22% C 6.63% H 6.82% N.

Found: 70.13% C 6.63% H 6.77% N.

EXAMPLE 25

1-[2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-5-methylphenyl]ethanone

A mixture of 6-fluoro-3-(-4-piperidinyl)-1,2-benzisoxazole hydrochloride (2.87 g, 11.23 moles), K_2CO_3 (2.5), 1-[2-(3-bromopropoxy)-5-methylphenyl]ethanone (3.74 g. 13.8 mmoles) in dimethylformamide (10 ml) and acetonitrile (50 ml) was heated at 95° C. for 6hr. At the end of the reaction, the solvent was concentrated and the mixture was extracted into dichloromethane (300 ml). The organic solution was washed with water and brine, dried over ($MgSO_4$) then concentrated down to a crude oil. The purification was done by flash chromatography over a silica gel column (SiO_2, 60 g, eluted with 1% CH_3OH:dichloromethane: 1.2 l; 3% CH_3OH:dichloromethane: 600 ml). The material thus obtained was crystallized from a small volume of ether and hexane to provide 2.13 gm (46%) of off-white 1-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-5-methylphenyl]ethanone, m.p.=92°–93° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3$: 70.22% C 6.63% H 6.82% N.

Found: 70.21% C 6.69% H 6.81% N.

EXAMPLE 26

N-[3-[3-]4(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4methoxyphenyl]acetamide hemifumarate

A mixture of 6-fluoro 3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (3.94 g, 15.4 moles), K_2CO_3 (3.67 g, 26.6 mmoles), N-[3-(3-bromopropoxy)-4-methoxyphenyl] acetamide (5.56 g: 18.6 mmoles) in dimethylformamide (75 ml) and acetonitrile (100 ml) was heated at 100° C. for 3hr. At the end of the reaction, the solvent was concentrated and the mixture was extracted into dichloromethane (500 ml). The organic solution was washed with water (500 ml) and brine (400 ml), dried, then concentrated to a crude oil. The purification was effected by flash chromatography over a silica gel column (SiO_2, 65 g, eluted with 1% CH_3OH:dichloromethane, 1.2 l; and 3% CH_3OH:dichloromethane, 500 ml). The material thus obtained weighed 2.33 g (34.3%) as an oil. This material was dissolved in ethanol treated with a solution of fumaric acid (661 mg) in ethanol. The N-[3-[3-[4-(5-fluoro-1,2 benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4methoxyphenyl]acetamide hemifumarate was obtained as off-white crystals weighing 2.17 g, m.p.=205°–206° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_4.0.5\ C_4H_4O_4$: 62.50% C 6.05% H 8.41% N.

Found: 62.30% C 6.03% H 8.32% N.

EXAMPLE 27

6-Chloro-3-(1-piperazinyl]-H-indazole

To a stirred suspension of 4-(-6-chloro-1-phenylsulphonyl-1H-indazol-3-yl)-1-piperazinecarbonitrile (192.5 g, 0.479 mol) in dry tetrahydrofuran (3.5 l) under N_2 was added, dropwise, $LiAlH_4$(958 ml of a 1.0M solution of lithium aluminum hydride in tetrahydrofuran; 0.958 mol. After complete addition, the reaction was heated to reflux and stirred under N_2 for 4hours. The reaction was cooled to 4° in an ice-salt bath and the excess lithium aluminum hydride was destroyed by the careful, dropwise addition of H_2O. The mixture was stirred vigorously for an additional 30 minutes and was then filtered through a coarse sintered glass funnel. The filter cake was washed well with tetrahydrofuran (3×500 ml) and then with methanol (2×500 ml) and the filtrate was concentrated to yield 1531.0 g of a beige gum. Trituration with diethyl ether afforded a solid, which was collected and dried to give 75.0 g (66%) of the desired indazole. A 4.0 g sample was recrystallized from toluene to

yield 3.2 g, which was recrystallized again from toluene (utilizing decolorizing carbon) to provide 21 g (35%) of a beige, 6-chloro-3-(1-piperazinyl)-1H-indazole solid, m.p.= 135°–137° C.

ANALYSIS

Calculated for $C_{11}H_{13}ClN_4$: 55.82% C 5.54% H 23.67% N.

Found: 55.91% C 5.54% H 23.41% N.

EXAMPLE 28

1-[4-[3-[4-(6-Fluoro-1H-indazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(-4-piperidinyl)-1H indazole (3.5 g, 0.016 mol) K_2CO_3 (2.2 g) 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (3.8 g, 0.016mol) and acetonitrile (90ml) was refluxed for 16 hours. The reaction was poured into water and the resulting white solid, which precipitated from solution, was collected to afford 5.5 g of the desired product. The compound was recrystallized from dimethylformamide (twice) to afford 3.0 g (44%) of 1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone as a white solid, m.p.=202°–204° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O3$: 67.75% C 6.63% H 9.88% N.

Found: 67.59% C 6.61% H 9.96% N.

EXAMPLE 29

1-[4-[3-[4-(6-Fluoro-1.2-benzisoxazol-3-yl)-1-piperidinyl]propoxy-3-methylphenyl]ethanone hemifumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (3.0 g; 11.7 moles), K_2CO_3 (3.0 g), 1-[4-(3-bromopropoxy)-3-methylphenyl]ethanone (3.19 g) in dimethylformamide (20ml) acetonitrile (50ml) was heated at 95° C. for 4 hr. At the end of the reaction, the solvent was concentrated down to about 30 ml, then partitioned between water (200 ml) and dichloromethane (300 ml). The dichloromethane solution was separated and washed with water and brine then dried over $MgSO_4$. The crude product from the evaporated solution was purified by flash chromatography over a silica gel column (SiO_2, 60 g, eluted with 1% methanol in ethane, 600 ml; 2% methanol in dichloromethane, 600 ml). The material thus obtained was a light yellow oil, weight: 2.07 g (43%). The oil was dissolved in ethanol and treated with a solution of fumaric acid (585 mg) in ethanol. The 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methylphenyl]ethanone hemifumarate crystals formed on cooling at 0° C. This was collected and weighed 1.5 g, m.p,=185°–187° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3.0.5\ C_4H_4$: 66.65% C 6.24% H 5.98% N.

Found 66.69% C 6.23% H 5.95% N.

EXAMPLE 30

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.27 g, 14.8 mmoles), K_2CO_3(3 g), 1-[4-(3-bromopropoxy)phenyl]ethanone (4.5 g, 17.5 mmoles) in acetonitrile (60 ml) was heated at reflux for 4 hr. The solvent was removed. The residue was dissolved in dichloromethane (300 ml) and washed with water and brine, then dried over $MgSO_4$. The crude product from the evaporated solution was purified by flash chromatography (SiO_2. 60 g; eluted with 1% methanol in dichloromethane, methane 1liter). The purest fractions were combined and gave 2.8 g, 48% of 1-[4-[3-[4-(6-fluoro-1,2benzisoxazol-3-yl)-1-piperidinyl] propoxy)phenyl]ethanone, m.p.=111°–112° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_3$: 69.68% C 6.36% H 7.07% N.

Found: 69.80% C 6.38% H 7.07% N.

EXAMPLE 31

1-[4-[3-[4(6-Chloro-1H-indazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone

A mixture of 6-chloro-3-(-1-piperazinyl)-1H-indazole (3.4 g, 0.014 mol), K_2CO_3 (2.5 g, 0.018 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (3.8 g, 0.016 mol), KI (200 mg), and acetonitrile (125 ml) was stirred at reflux under N_2 for 30 hours. Alter standing at room temperature for 40 hours, the reaction was filtered and the filter cake was washed well with acetonitrile. The filtrate was concentrated to an oily solid, which was partitioned between water and ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$, and concentrated to yield 6.9 g of a dark oil, which solidified after 2days under vacuum. The product was purified by preparative HPLC (Waters Associates Prep LC/system 500 utilizing 2silica gel columns and 6% methanol/methylene chloride as eluent) to yield 4.2 g. The material was recrystallized from ethanol to yield 3.4 g of glistening, beige, 1-[4-[3-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]propoxy)-3-methoxyphenyl] ethanone crystals, m.p.=132°–134° C.

ANALYSIS

Calculated for $C_{23}H_{27}ClN_4O_3$: 62.37% C 6.14% H 12.65% N.

Found: 62.49% C 6.16% H 12.60% N.

EXAMPLE 32

1-[4-[4-[4-(1,2-Benzisothiazol-3-yl-1-piperazinyl] butoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(1-piperazinyl)-1.2-benzisothiazole (4.0 g, 0.0182 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl] ethanone (6.0 g. 0.0218 mol). KI (200 mg), and acetonitrile (125 ml) was stirred at reflux under N_2 for 5hours. Most of the solvent was removed in vacuo and the resultant gummy residue was partitioned between ethyl acetate and-water. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to yield 7.8 g. Purification by preparative HPLC (Waters Associates Prep LC/System 500, utilizing 2silica gel columns and 4% methanol-methylene chloride an eluent) afforded 6.5 g of a damp, off-white solid. The product was recrystallized twice from toluene to provide 3.1 g (39%) of 1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-butoxy]-3methoxyphenyl ethanone as a white solid. m.p.=114°–116° C.

ANALYSIS

Calculated for $C_{24}H_{29}N_3O_3S$: 65.58% C 6.65% H 9.36% N.

Found: 65.74% C 6.66% H 9.54% N.

EXAMPLE 33

4-[3-[4-(-6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzonitrile

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 mmoles), K_2CO_3 (2.8 g)-4-(3-

bromopropoxy)-3-methoxybenzonitrile (4.0 gm, 14.8 mmoles) is acetonitrile (70ml) was heated at reflex for 3hr. At the end of the reaction, the solvent wet removed on a rotary evaporator. The organic material was extracted into dichloromethane (50 ml) and the inorganics were filtered off. The dichloromethane solution was concentrated to a crude oil. The purification was done by flash chromatography over a silica gel column (SiO_2, 55 gm; eluted with dichloromethane, 600 ml; 1% methanol in dichloromethane, 600 ml). The material thus obtained was crystallized from a small amount of dichloromethane. Recrystallization from ethanol (25ml) provided 3.8 m (68%) of 4-[3-[4-(-6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzonitrile as white crystals. m.p.=107°–108° C.

ANALYSIS

Calculated for $C_{23}H_{24}FN_3O_3$: 67.47% C 5.91% H 10.26% N.

Found: 67.32% C 5.90% H 10.24% N.

EXAMPLE 34

1-[4-[4-[4-(6-Fluoro-1H-indazol-3-yl)-1-piperidinyl]-butoxy]-3-methoxyphenyl]ethanone

A stirred of mixture of 6-fluoro-3-(4-piperidinyl)-1H-indazole (1.9 g, 0.0086 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone 2.6 g, 0.0086 mol), K_2CO_3 (1.2 g), and acetonitrile (7.5 ml) was refluxed for 6 hr. The reaction was poured into water and a white solid settled from solution. This was collected, dried and afforded 3.2 g of product. The product was recrystallized from ethanol to yield 2.7 g (71%) of 1-[4-[4-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl]butoxy-3-methoxyphenyl]ethanone as glistening white flakes, m.p.=158°–160° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_3$: 68.32% C 6.88% H 9.56% N.

Found: 68.00% C 6.93% H 9.51% N.

EXAMPLE 35

1-[4-[3-[4-(1-Benzoyl-6-fluoro-1H-indazol-3-yl)-1-piperizinyl]propoxy]-3-methoxyphenyl]ethanone sesquifumarate

A mixture of 1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone (3.2 g, 0.0073 mol) and benzoyl chloride (15ml) was heated on a steam bath for 15 min. The reaction was allowed to cool and ether was added. The insoluble off white compound was harvested to yield 4.4 g of the product as a hydrochloride salt. The salt was converted to free base with aqueous ammonium hydroxide, and after extractive workup with methylene chloride, 3.0 g of the free base was isolated as a white solid. The free base was dissolved in ethyl acetate and fumaric acid (0.72 g, 1.1 eq) was added and the mixture heated on the steam bath for 15 min. After standing at ambient temperature for 4days, 2.0 g of an off-white fumarate salt was collected, while concentration of the filtrate afforded an additional 1.0 g of the salt. Recrystallization, first from ethyl acetate, and then from ethanol yielded 1.4 g (26%) of 1-[4-[3-[4(1-benzoyl-6-fluoro-1H-indazol-3-yl)-1-piperazinyl)-propoxy)-3-methoxyphenyl]ethanone sesquifumarate, m.p.=138°–140° C.

ANALYSIS

Calculated for $C_{30}H_{31}FN_4O_4.1.5C_4H_4O_4$: 61.35% C 5.29% H 7.95% N.

Found: 61.68% C 5.31% H 8.25% N.

EXAMPLE 36

1-[4-[4-[4-(6-Chloro-1H-indazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone

A mixture of 6-chloro-[3-(1-piperazinyl)]-1H-indazole (4.0 g, 0.017 mol), K_2CO_3 (2.8 g, 0.0020 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (5.7 g, 0.019 mol), KI (100 mg) and acetonitrile (125 ml) was stirred at reflux under nitrogen for 18 hrs. The cooled reaction was poured into water and the resultant off-white solid was collected by filtration and dried to yield 7.0 g. The compound was recrystallized twice from toluene to yield 6.2 g. Further, purification by preparative HPLC (Waters Associates Prep LC/System 500, utilizing 5% methanol/methylene chloride as eluent and 2 silica gel columns) afforded 5.3 g of glistening, beige crystals, which were recrystallized four times from toluene to yield 3.1 g of a white solid. Analytically pure material was obtained by a subsequent recrystallization from dimethylformamide to afford 2.5 g (32%) of 1-[4-[4-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone as an off-white powder, m.p.=189°–191° C.

ANALYSIS:

Calculated for $C_{24}H_{29}ClN_4O_3$: 63.08% C 6.40% H 12.26% N.

Found: 62.86% C 6.57% H 12.49% N.

EXAMPLE 37

1-[4-[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone hemifumarate

A mixture of 3-(1-piperazinyl)-1,2-benziothiazole (4.0 g, 0.0182 mol), K_2CO_3 (3.0 g, 0.0218 mol), KI (200 mg), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (5.3 g, 0.0200 mol), and acetonitrile (125 ml) was stirred at reflux under N_2 for 26 hours. The cooled reaction was filtered and the filter cake was washed well with acetonitrile. The filtrate was concentrated to afford 10.7 g of an oily residue, which was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$ and concentrated to yield 8.0 g of a dark oil. The oil was purified by preparative HPLC (Waters Associates Prep LC/System 500, utilizing 2 silica gel columns and 3% methanol/methylene chloride as eluent). Concentration of appropriate fractions provided 4.6 g of a red oil, which solidified upon standing. A 3.4 g sample was taken up in ethyl acetate (100 ml) and fumaric acid (0.95 g) was added. The mixture was stirred at a mild reflux for 1 hour and then at ambient for 1.5 hours. The resultant beige solid was collected by filtration and dried to yield 4.0 g. The product was recrystallized twice from ethanol to provide 2.7 g (27%) of 1-[4-[3-[4-(1-benzisothiazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone hemifumarate as a beige powder, m.p.=186°–188° C.

ANALYSIS

Calculated for $C_{23}H_{27}N_3O_3S.0.5\ C_4H_4O_4$: 62.09% C 6.06% H 8.69% N.

Found: 62.01% C 6.06% H 8.68% N.

EXAMPLE 38

1-[3,5-Dibromo-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.0 g, 9.0 mmoles), K_2CO_3 (1.3), and 1-[4-(3-bromopropoxy)-3,5-dibromophenyl]ethanone (2.65 g, 9.0 mmoles) and acetonitrile (50 ml) was heated at reflux for 3 hr. At the end of the reaction, the solvent was evaporated and the residue was extracted into dichloromethane (150 ml). The insolubles were filtered off. The dichloromethane solution was concentrated down to an oil. The purification was done by flash chromatography on a silica gel column (SiO_2, 47 g; eluted with dichloromethane,

300 ml; 1% methanol in dichloromethane, 600 ml). The material thus purified as a colorless oil, solidified on standing. Recrystallization from ethanol gave 1-[3,5-dibromo-4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl)-1-piperidinyl) propoxy]phenyl]ethanone as white crystals (2.93 g, 57%), m.p. 102°–103° C.

ANALYSIS

Calculated for $C_{23}H_{23}Br_2FN_2O_3$; 49.84% C 4.18% H 5.05% N.

Found: 49.91% C4.11% H 4.98% N.

EXAMPLE 39

1-[4-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl] ethoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(1-piperazinyl)-1,2-benzisothiazole (4.0 g, 0.0182 mol), 1-[4-(2-chloroethoxy)-3-methoxyphenyl] ethanone (4.3 g, 0.0200 mol), K_2CO_3 (3.0 g, 0.0218 mol), acetonitrile (125 ml) and a catalytic amount of KI was heated to reflux and stirred under nitrogen for 24 hours. At this point, an additional amount of K_2CO_3 (1.0 g, 0.0072 mmol) and alkylating agent (0.4 g, 0.0017 mol) was added to the reaction mixture and heating at reflux was resumed for 24 hours. The reaction was cooled to ambient temperature and filtered. The filter cake was washed with acetonitrile and the filtrate was concentrated to afford a dark oil. The oil was extracted with methylene chloride, and the organic extract was washed with water, dried with $MgSO_4$ and concentrated to yield 9.2 g of an oil. Purification by preparative HPLC (Waters Associates Prep LC/System 500 utilizing 2 silica gel columns and 3% methanol/methylene chloride as eluent) provided 3.8 g of a soft, beige gum, which readily solidified. The compound was recrystallized twice from ethanol to give 2.1 g (28%) of 1-[4-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethoxy]-3-methoxyphenyl]ethanone as a beige solid, m.p.=98°–100° C.

ANALYSIS

Calculated for $C_{22}H_{25}N_3O_3S$: 64.21% C 6.12% H 10.21% N.

Found: 64.05% C 6.09% H 10°–12% N.

EXAMPLE 40

6-Fluoro-3-[1-(3-phenoxypropyl)-4-piperidinyl]-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzoisoxazole (4.0 g, 0.0182 mol), K_2CO_3 (3.0 g, 0.0218 mol), KI (100 mg), 3-chloropropoxybenzene (3.4 g, 0.0200 mol), and acetonitrile was stirred at reflux under nitrogen for 30 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried with $MgSO_4$ and concentrated to afford 6.2 g of a damp, beige solid. The compound was recrystallized twice from ethanol to yield (47%) of 6-fluoro-3-[1-(3-phenoxypropyl)-4-piperidinyl]-1,2-benzisoxazole as a light beige solid, m.p.=78°–80° C.

ANALYSIS

Calculated for $C_{21}H_{23}FN_2O_2$: 71.17% C 6.54% H 7.90% N.

Found: 71.00% C 6.52% H 7.81% N.

EXAMPLE 41

1-[4-[2-[4-(6-Chloro-1H-indazol-3-yl)-1-piperazinyl]ethoxy]-3-methoxyphenyl]ethanone

A mixture of 6-chloro-[3-(1-piperazinyl)-1H-indazole (2.1 g, 0.0089 mol), $K_{2\ CO3}$ (1.5 g, 0.0107 mol), KI (100 mg), 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone (2.2 g, 0.0098 mol) and acetonitrile (70 ml) was stirred at reflux for 48 hours under N_2. The cooled reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic extract was washed with water, dried with $MgSO_4$ and concentrated to yield 6.0 g of a light yellow oil. The oil was purified by preparative HPLC (Waters Associates prep LC/System 500, employing 2 silica gel columns and 5.5% methanol/methylene chloride as eluent). Concentration of later fractions provided 1.6 g of an off-white solid. This was combined with an additional sample (3.4 g total) and two consecutive recrystallizations from ethanol yielded 2.1 g (23%) of 1-[4-[2-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]ethoxy]-3-methoxyphenyl] ethanone an off-white solid, m.p.=154°–156° C.

ANALYSIS

Calculated for $C_{22}H_{25}ClN_4O_3$: 61.61% C 5.88% H 13.06% N.

Found: 61.66% C 5.87% H 13.06% N.

EXAMPLE 42

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyhenyl]-2,2,2-trifluoroethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (1.5 g, 0.0067 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone (2.0 g, 0.0067 mol), K_2CO_3 (0.88), KI (0.1) and acetonitrile (50 ml) was stirred and refluxed for 16 h. After cooling, the reaction was poured into water and the aqueous mixture extracted with ethyl acetate. The extract was washed (H_2O), dried ($MgSO_4$), and the solvent was concentrated to an oil, which upon evacuation at high vacuum afforded 3.2 g of a waxy solid. The solid was chromatographed on a Waters preparative LC (silica columns, eluting with 3% methanol-dichloromethane). Concentration of the appropriate fractions gave 1.8 g (56%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]-2,2,2-trifluoroethanone solid, m.p.= 94°–96° C.

ANALYSIS

Calculated for $C_{24}H_{24}F_4N_2O_4$: 60.00% C 5.03% H 5.83% N.

Found: 60.01% C 5.06% H 5.68% N.

EXAMPLE 43

1-[4-8 3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl]-1-piperidinyl]propoxy]-3-methylmercaptophenyl] ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (1.88 g, 8.5 mmoles), K_2CO_3 (1.8 g) and 1-[4-(3-bromopropoxy)-3-methylmercaptophenyl]ethanone (2.3 g, 7.6 mmole) in acetonitrile (100 ml) was heated at reflux for 4 hr. At the end of the reaction, the solvent was concentrated, then diluted with dichloromethane (250 ml). The insolubles were filtered off. The dichloromethane solution was concentrated to dryness as an oil. Purification was effected by flash chromatography on a silica gel column (SiO_2, 54 g, eluted with dichloromethane, 500 ml; 1% methanol:dichloromethane, 1.1 l). The purest fractions were combined to give a colorless oil which solidified to an off-white solid (2.4 g). Recrystallization from ethanol (100 ml) yielded 1-[4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl]-1-piperidinyl]propoxy]-3-methylmercaptophenyl]ethanone as off-white needle crystals, 2.15 g, m.p.=150°–152° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3S$: 65.14% C 6.15% H 6.33% N.

Found: 65.09% C 6.10% H 6.25% N.

EXAMPLE 44

1-[4-(3-Bromopropoxy)-3-bromophenyl]ethanone

A stirred mixture of 3-bromo-4-hydroxyacetophenone (4.5 g, 21.2 mmoles), K_2CO_3 (4 g) and 1,3-dibromopropane (7.6 g) in acetonitrile (200 ml) was heated at reflux for 2 hr. At the end of the reaction, the solvent was removed and the residue was dissolved in dichloromethane (400 ml) and filtered. The dichloromethane solution was concentrated to an oil. The oil was added to isopropyl ether and stirred to cause crystallization (4.1 g; 58%). The solid was recrystallized from isopropyl ether to give 3.5 g of 1-[4-(3-bromopropoxy)-3-bromophenyl]ethanone as glistening crystals, m.p.=83°–84° C.

ANALYSIS

Calculated for $C_{11}H_{12}Br_2O_2$: 39.31% C 3.60% H.

Found: 39.80% C 3.55% H.

EXAMPLE 45

1-[4-(3-Bromopropoxy)-3,5-dibromophenyl] ethanone

A stirred mixture of 3,5-dibromo-4-hydroxyacetophenone (3.0 g, 10.1 mmole), K_2CO_3 (2.8 g, 20.3 mmoles), 1,3-dibromopropane (4.0 g, 19.8 moles) in acetonitrile (100 ml) was heated at reflux for 5 hr. The solvent was removed. The crude product was extracted into dichloromethane (150 ml) and the insoluble inorganics were filtered off. The solution was concentrated to dryness again. Purification was carried out by flash chromatography on silica gel (45 g, SiO_2; eluted with 1:1 hexane:dichloromethane). The material thus obtained (2.8 g) was recrystallized twice from isopropyl ether to give analytically pure 1-[4-(3-bromopropoxy)-3,5-dibromophenyl]ethanone, m.p.=87°–88° C.

ANALYSIS

Calculated for $C_{11}H_{11}Br_3O_2$: 31.84% C 2.67% H.

Found: 31.97% C 2.63% H.

EXAMPLE 46

1-[4-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperidinyl] butoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 3-(4-piperidinyl)-1,2-benzisothiazole (2.6 g, 0.0119 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (3.9 g, 0.0131 mol), K_2CO_3 (2.0 g, 0.0143 mol), KI (200 mg) and acetonitrile (125 ml) was stirred at reflux under nitrogen for 18 hours. The reaction was cooled to ambient temperature and filtered. The filter cake was washed well with fresh acetonitrile and the filtrate was concentrated to yield a wet, brown solid. The residue was diluted with water and the aqueous suspension was extracted with methylene chloride. The organic extract was washed with water, dried with $MgSO_4$ and concentrated to afford 6.5 g of a dark oil. The oil was purified by preparative HPLC (Waters Associates prep LC/System 500, utilizing 2 silica gel columns and 5% methanol/methylene chloride) to give 4.5 g of a beige solid. A 3.1 g (0.0071 mol) sample was taken up in absolute ethanol (80 ml) and oxalic acid (1.67 g, 0.0074 mol) was added. The solution was refluxed mildly on a stream bath for 45 minutes and was then stirred at ambient temperature for 1 hour. The resultant suspension was diluted with anhydrous ether (150 ml) and stirred for 5 minutes. The solid was collected and dried to afford 3.1 g of a light, beige solid. The salt was recrystallized from ethanol to yield 2.8 g. The compound was converted back to the free base with 50% NaOH to give 2.4 g, which was immediately recrystallized from ethanol to provide 1.5 g (29%) of 1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone as a beige powder, m.p.=78°–80° C.

ANALYSIS

Calculated for $C_{25}H_{30}N_2O_3S$: 68.46% C 6.91% H 6.39% N.

Found: 68.34% C 6.85% H 6.33% N.

EXAMPLE 47

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl] phenylmethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10 mmoles), K_2CO_3 (2.3 g) and 1-[4-(3-bromopropoxy)-3-methoxyphenyl] phenylmethanone (3.47 g, 10 mmoles) in acetonitrile (100 ml) was heated at reflux for 3 hours. At the end of reaction, the acetonitrile was concentrated and the mixture was extracted into dichloromethane (200 ml). The insolubles were filtered off and the solvent was evaporated to an oil. Purification was carried out by flash chromatography over a silica gel column (SiO_2, 50 g; eluted with dichloromethane, 600 ml; 1% methanol:dichloromethane, 600 ml; 2% methanol: 98% dichloromethane, 600 ml). The fractions containing the pure product were combined and concentrated to give 4.24 g (87%) of an off-white solid. Recrystallization from ethanol (75 ml) gave 3.9 g of 1-[4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methyoxyphenyl]phenylmethanone as off-white crystals, m.p.=128°–130° C.

ANALYSIS

Calculated for $C_{29}H_{29}FN_2O_4$: 71.30% C 5.98% H 5.73% N.

Found: 71.31% C 5.99% H 5.75% N.

EXAMPLE 48

1-[4-[3-[4-(6-Fluoro-1,2-benziosoxazol-3-yl)-1-piperidinyl]propoxy]-3-bromophenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.1 g, 9.5 mmole), K_2CO_3 (2.0 g) 1-[3-bromo-4-(3-bromopropoxy)phenyl]ethanone (3.1 g, 9.2 mmoles) in acetonitrile (100 ml) was heated at reflux for 3 hours. At the end of reaction, the solvent was concentrated and the mixture was extracted into dichloromethane (200 ml). The insolubles were filtered off. The dichloromethane was concentrated again. The crude residue was purified by flash chromatography over a silica gel column (SiO_2, 49 g; eluted with dichloromethane, 500 ml; 1% methanol:dichloromethane, 600 ml; 3% methanol: 97% dichloromethane, 600 ml). The material thus obtained (3.26 g, 72%) was recrystallized from ethanol (40 ml) to give 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-bromophenyl]ethanone as light yellow crystals (3.0), m.p.=126°–128° C.

ANALYSIS

Calculated for $C_{23}H_{24}BrFN_2O_3$: 58.12% C 5.09% H 5.89% N.

Found: 57.64% C 5.35% H 5.55% N.

EXAMPLE 49

3-[1-[3-[4-(1-Ethoxyethyl)-2-methoxyphenoxy] propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole hydrochloride

To a mixture of 4-[3-[4-(6-fluoro-1,2-benzisoxazole-3-yl)-1-piperidinyl]propoxy]-3-methoxy-α-

methylbenzenemethanol (3.8 g, 0.089 mol) in pyridine (25 ml) was added acetic anhydride (5 ml). The mixture was warmed briefly on the steam bath to effect solution, and then the reaction was allowed to stand at ambient temperature for 16 hours. Most of the pyridine was evaporated under reduced pressure and the resultant oil was diluted with water. The aqueous solution was made basic with dilute NaOH, and subsequently extracted with ethyl acetate. The organic extract was washed (water), dried ($MgSO_4$), and the solvent concentrated to give 3.7 g of the O-acetyl derivative as a colorless oil. The compound was dissolved in diethyl ether and ethereal HCl was added to precipitate a gum-like hydrochloride salt, which upon treatment with refluxing ethyl acetate afforded 3.4 g of a crystalline salt, m.p. 143°–145° C. Attempting to recrystallize the salt from ethanol:diethyl ether resulted in displacement of the acetate to afford the ethyl ether. The salt of this product (2.8 g) was recrystallized from ethanol:diethyl ether to yield 2.1 g (48%) of 3-[1-[3-[4-(1-ethoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole hydrochloride, m.p.=139°–141° C.

ANALYSIS

Calculated for $C_{26}H_{33}FN_2O_4.HCl$: 63 . 34% C 6.95% H 5.68% N.

Found: 63.06% C 6.80% H 5.63% N.

EXAMPLE 50

3-[1-[3-[4-(1-Acetoxyethyl)-2-methoxyphenoxy] propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole fumarate

A mixture of 4-[3-[4-(6-fluoro-1,2-benzisoxaol-3-yl)-1-piperidinyl]-3-methoxy-α-methylbenzenemethanol (4.8 g, 0.011 mol) in pyridine (45 ml) was warmed briefly to effect solution and then acetic anhydride (6.3 ml) was added. The reaction stood at ambient temperature for 16 hours, was concentrated in vacuo, and the colorless oil that remained was dissolved in water. The aqueous solution was made basic with saturated K_2CO_3 solution, and the mixture was extracted with diethyl ether. The extract was washed (water), dried ($MgSO_4$) and concentrated to afford 5.2 g of a thick, colorless oil. The oil (4.8 g) was dissolved in anhydrous diethyl ether and fumaric acid (1.2 g, 0.01 mol) was added. The mixture was stirred at ambient temperature for 4 hours, and then was permitted to stand at ambient temperature for 16 hours. The resultant white, 3-[1-[3-[4-(1-acetoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1, 2benzisoxazole fumarate was collected and afforded 3.0 g of material. The filtrate was treated with an additional amount of fumaric acid (0.3) and 0.9 g more of 3-[1-[3-[4-(1-acetoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole fumarate was harvested. The two batches were combined and recrystallized from acetonitrile (twice) to yield 2.3 g (43%) of the acetate, m.p.=150°–152° C.

ANALYSIS

Calculated for $C_{26}H_{31}FN_2O_3.C_4H_4O_4$: 61.43% C 6.01% H 4.78% N.

Found: 61.06% C 5.87% H 4.73% N.

EXAMPLE 51

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]pentanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 0.01 mole), K_2CO_3 (3 g), 1-[4-(3-bromopropoxy)-3-methoxyphenyl]pentanone (3.7 g, 0.0113 mole) in acetonitrile (140 ml) was heated at reflux for 4 hours. At the end of the reaction, the mixture was cooled and filtered. The filtrate was concentrated to an oil. Purification was performed by flash chromatography over a silica gel column (SiO_2, 55 g; eluted with 1% methanol in dichloromethane, 600 ml; 3% methanol: 97% dichloromethane, 400 ml). The fractions containing pure product were pooled and concentrated to a solid (4.3 g, 91%). Recrystallization from ethanol (10 ml) gave a powdery solid of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]pentanone (3.22), m.p.=79°–80° C.

ANALYSIS

Calculated for $C_{27}H_{33}FN_2O_4$: 69.21% C 7.10% H 5.98% N.

Found: 69.00% C 6.94% H 6.39% N.

EXAMPLE 52

2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-N-methylbenzenamine hemifumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.5 g, 0.0114 mol), K_2CO_3 (1.8 g, 0.0130 mol), 4-(3-chloropropoxy)-2-methylaminobenzene (2.4 g, 0.0120 mol) and acetonitrile (100 ml) was stirred at reflux for 18 hours. The reaction was cooled to ambient temperature and was poured into water. The aqueous mixture was extracted with ethyl acetate and the ethyl acetate extract was washed with water, dried with $MgSO_4$, and concentrated to yield 4.1 g of a brown oil. The oil was purified by preparative HPLC (Waters Associates prep LC/System 500, utilizing 2 silica gel columns and eluting with 4% methanol-methylene chloride). Concentration of appropriate fractions yielded 2.45 g of a beige oil. The product was taken up in ethyl acetate (50 ml) and fumaric acid (0.78 g) was added. The mixture was stirred at mild reflux for 45 minutes and then at ambient temperature for 1.5 hours. The product was isolated by vacuum filtration to provide 2.5 g of a pale yellow solid. Recrystallization from ethanol afforded 2.0 g (40%) of 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-N-methylbenzenamine hemifumarate as beige crystals, m.p.=180°–182° C.

ANALYSIS

Calculated for $C_{22}H_{26}FN_3O_2.0.5C_4H_4O_4$: 65.28% C 6.40% H 9.52% N.

Found: 65.08% C 6.35% H 9.45% N.

EXAMPLE 53

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]propanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.8 g, 15.2 mmoles), K_2CO_3 (3), 1-[4-(3-bromopropoxy)-3-methoxyphenyl]propanone (4.6 g, 18.2 mmoles) in acetonitrile (100 ml) was heated at reflux for 2 hours. At the end of the reaction, the mixture was filtered and the solvent was concentrated and the residue was extracted into dichloromethane (300 ml). The dichloromethane was filtered and concentrated again. The crude material (6.4) was purified by flash chromatography over a silica gel column (SiO_2, 50 g; eluted with dichloromethane, 700 ml; 1% methanol in dichloromethane, 1.4 l). The material thus purified (weight: 2.87 g, 51%) was recrystallized from ethanol (25 ml) to give 2.13 g of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]propanone as beige colored crystals, m.p.= 118°–119° C.

ANALYSIS

Calculated for $C_{25}H_{29}FNO_2O_4$: 68.16% C 6.64% H 6.36% N.

Found: 68.32% C 6.63% H 6.29% N.

EXAMPLE 54

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzamide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10.0 mmoles), K_2CO_3 (2.0 g) and 4-(3-bromopropoxy)-3-methoxybenzamide (2.32 g, 8.0 moles) in acetonitrile (80 ml) was heated at reflux for 5 hours. At the end of the reaction the solvent was evaporated. The residue was extracted into dichloromethane. The inorganic insolubles were filtered off. The dichloromethane was concentrated again. The crude residue was purified by flash chromatography over a silica gel column (55 g, SiO_2; eluent with 1% methanol in dichloromethane, 1 l; 2% methanol in dichloromethane, 1 l). The material thus obtained weighed 2.93 g (84%) as white crystals. Recrystallization from the hot ethanol (60 ml) gave 2.2 g of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide as white crystals, m.p.=163°–164° C.

ANALYSIS

Calculated for $C_{23}H_{26}FN_3O_4$: 64.62% C 6.13% H 9.83% N.

Found: 64.20% C 6.06% H 9.71% N.

EXAMPLE 55

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy-]-3-(methylamino)phenyl] ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.3 g, 0.0103 mol), K_2CO_3 (1.4 g, 0.0103 mol), 1-[4-(3-chloropropoxy)-3-(methylamino)phenyl] ethanone (2.5 g, 0.0103 mol), KI(0.10), and acetonitrile (100 ml) was stirred at reflux under nitrogen for 23 hours. The reaction was cooled to ambient temperature, poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed twice with water, dried with $MgSO_4$ and was concentrated to yield 4.8 g of a damp, brown solid. The compound was isolated by preparative HPLC (Waters Associates prep LC/System 500, utilizing 2 silica gel column and 4% methanol-methylene chloride as eluent). Concentration of appropriate fractions afforded 2.4 g. Recrystallization from ethanol gave 2.1 g of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-(methylamino)phenyl]ethanone as a beige solid, m.p.=151°–153° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_3$: 67.75% C 6.63% H 9.88% N.

Found: 67.83% C 6.76% H 9.90% N.

EXAMPLE 56

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-ethoxyphenyl]ethanone

A suspension of NaH (0.28 g of a 50% oil dispersion, 0.0059 mol) in dimethylformamide (20 ml) was cooled to 4° C. in an ice bath. To this was added, dropwise, 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone (2.3 g, 0.0056 mol) dissolved in dimethylformamide (40 ml). After total addition, the mixture was stirred under nitrogen for 1 hr. keeping the temperature below 10° C. A solution of bromoethane (1.3 g, 0.0118 mol) dissolved in dimethylformamide (15 ml) was then added, dropwise, to the reaction mixture. Stirring under nitrogen was continued for 3 hours allowing the temperature to slowly rise to ambient temperature. The reaction was cooled in an ice bath, water was added and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$, and was concentrated to yield 3.9 g of a damp, beige solid. The solid was triturated with diethyl ether and filtered to yield 1.5 g. This was combined with an additional sample (3.5 g total), and recrystallization from ethanol provided 3.0 g (57%) of glistening, beige crystals of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-ethoxyphenyl] ethanone, m.p.=112°–114° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_4$: 68.16% C 6.64% H 6.36% N.

Found: 68.10% C 7.03% H 6.35% N.

EXAMPLE 57

1-[4-(3-Bromopropoxy)-3-(methylmercapto)phenyl] ethanone

A mixture of 1-[4-hydroxy-3-(methylmercapto)phenyl] ethanone (5.4 g; 0.03 mole), K_2COO_3 (4.2 g), 1,3-dibromopropane (8 g, 0.039 mole) in acetonitrile (150 ml) was heated at reflux for 3 hours and stirred at room temperature overnight. Acetonitrile was removed at reduced pressure and the residue was extracted into dichloromethane (250 ml). Insolubles were filtered off. The dichloromethane solution was concentrated. The crude product was purified on a silica gel columns (SiO_2, 100 g; eluted with 3:2 hexane:dichloromethane, 1.6 l). The compound crystallized upon concentration, and the product (3.5 g, 39%) was recrystallized from ethanol (40 ml) to yield 1-[4-(3-bromopropoxy)-3-(methylmercapto)phenyl]ethanone as white needles, 2.0 g; m.p.=120°–122° C.

ANALYSIS

Calculated for $C_{12}H_{15}BrO_2S$: 47.53% C 4.99% H.

Found: 47.74% C 4.91% H.

EXAMPLE 58

4-(3-Bromopropoxy)-3-methoxybenzonitrile

A mixture of 4-hydroxy-3-methoxybenzonitrile (7.5 g, 50 mmoles), K_2CO_3 (12.5), and 1,3-dibromopropane (15 g, 75 moles) in acetonitrile (100 ml) was heated at reflux for 3 hours and left standing at room temperature overnight. The solvent of the reaction was removed on a rotary evaporator, and the crude solid was extracted into methylene chloride (500 ml). The insolubles were filtered off. The dichloromethane solution was concentrated and the material was purified on a flash chromatography columns (SiO_2, 105 g; eluted with 2:3 dichloromethane:hexane, and then with dichloromethane). The desired product thus purified weighed 7.74 g (52%). Recrystallization twice from ethanol gave analytically pure 4-(3-bromopropoxy)-3-methoxybenzonitrile, m.p.=99°–101° C.

ANALYSIS

Calculated for $C_{11}H_{12}BrNO_2$: 48.91% C 4.88% H 5.19% N.

Found: 49.49% C 4.47% H 5.21% N.

EXAMPLE 59

1-[4-(3-Bromopropoxy)-3-methylphenyl]ethanone

A mixture of 4-hydroxy-3-methylacetophenone (14.5 g, 96 moles), K_2CO_3 (17.5 g, 144 mmoles), and 1,3-

dibromopropane (30 g, 144 mmoles) in acetonitrile) 400 ml) was heated at reflux for 6 hours. At the end of the reaction, the solvent was removed on a rotary evaporator, and the crude solid was extracted into dichloromethane (750 ml). The insoluble inorganics were filtered off. The dichloromethane solution was concentrated again to a crude oil (34.5 g). Purification was effected by flash chromatography over a silica gel column (SiO_2, 150 g; eluted with 7:3 hexanes:dichloromethane, 2 l; and dichloromethane 2 l). The material thus purified weighted 14.6 g (56%) and was recrystallized from ethanol. Recrystallization again from ethanol gave analytically pure 1-[4-(3-bromopropoxy)-3-methylphenyl]ethanone, m.p.=59°–61° C.

ANALYSIS

Calculated for $C_{12}H_{15}BrO_2$: 53.15% C 5.58% H.

Found: 53.35% C 5.52% H.

EXAMPLE 60

1-[4-(3-Bromopropoxy)-3-methoxyphenyl] phenylmethanone

A mixture of 1-(4-hydroxy-3-methoxyphenyl) phenylmethanone (14 g, 61.4 mmoles), K_2CO_3 (13 g, 92.1 mmoles), and 1,3-dibromopropane (28 g, 86 moles) in acetonitrile (400 ml) was heated at reflux for 4 hours. The reaction was followed by thin layer chromatography. At the end of the reaction, the inorganics were filtered off and the solvent was removed on a rotary evaporator. The residue was purified on a flash chromatographic column (SiO_2, 140 g, eluted with 4:1 hexane:dichloromethane, 1.2 l) to give a partially solidified material: 15.44 g (72%). Recrystallization twice from ethanol gave 2.84 g of 1-[4-(3-bromopropoxy)-3-methoxyphenyl]phenylmethanone as white crystals, m.p.=88°–89° C.

ANALYSIS

Calculated for $C_{17}H_{17}BrO_3$: 58.74% C 4.91% H.

Found: 59.03% C 4.87% H.

EXAMPLE 61

N-[2-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide

(A) N-[2-(3-phenylsulfonyloxypropxoy)phenyl] acetamide

To a solution of N-2-[2-(3-hydroxypropoxy)phenyl] acetamide (Example 113) (7.5 g, 0,036 mol) in pyridine (90 ml), cooled to 0° C., was added p-toluenesulfonyl chloride (13.6 g, 0.056 mol). After the tosyl chloride went into solution, the reaction was then allowed to stand at 5° C. for 16 hours. The reaction was poured onto ice, and a brown oil settled. The aqueous supernatant was decanted from the oil, and the residual oil taken up in diethyl ether. The diethyl ether was washed with cold (5° C.) 3N HCl and then with brine. The organic layer was dried ($MgSO_4$), and concentrated to afford a thick, brown oil, 5.3 g.

(B) N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.4 g, 0.016 mol), N-[2-(3-phenylsulfonyloxypropoxy)phenyl]acetamide (5.3 g, 0.016 mol), K_2CO_3 (2.2 g), and acetonitrile (50 ml) was stirred and refluxed for 5 hours. The reaction was poured into water, and the aqueous suspension was extracted with ethyl acetate. The ethyl acetate was washed (water and brine), dried ($MgSO_4$) and the solvent was concentrated to afford 6.0 g of a thick, brown oil. The oil was chromatographed on a Waters Prep 500 LC on silica gel. Concentration of the appropriate fractions afforded 3.0 g of a beige solid. This was recrystallized from ethyl acetate to yield (with concentration of the mother liquors) 2.2 g (33%) of N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl] acetamide as a beige solid, m.p.=118°–120° C.

ANALYSIS

Calculated for $C_{23}H_{26}FN_3O_3$: 67.14% C 6.37% H 10.21% N.

Found: 67.06% C 6.43% H 10.23% N.

EXAMPLE 62

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-dimethylaminophenyl] ethanone

(A) 1-[4-(3-Chloropropoxy)-3-dimethylaminophenyl]ethanone

To a suspension of sodium hydride (2.3 g, 0.0485 mol of 50% oil dispersion) with dimethylformamide (75 ml), and cooled to 3° in an ice-salt bath and under a stream of nitrogen was added, dropwise, 1-(4-hydroxy-3-dimethylaminophenyl)ethanone (8.7 g, 0.0485 mol) dissolved in dimethylformamide (150 ml) so that the temperature did not go over 7°. After the addition was over, the bath was removed and the reaction was stirred at ambient temperature for 45 minutes. The ice bath was reapplied and a solution of 1-bromo-3-chloropropane (8.4 g, 0.0534 mol) in dimethylformamide (25 ml) was added dropwise. After the addition was complete, the reaction was stirred for 18 hours at ambient temperature under nitrogen. The reaction was chilled to 7° in an ice bath and water (200 ml) was carefully added. After stirring for 5 minutes, the aqueous mixture was extracted with ethyl acetate (5x200 ml). The ethyl acetate extract was washed with water (2x50 ml), dried with $MgSO_4$, and concentrated to yield 22.2 g of a black oily liquid. The compound was purified by prep HPLC, and combination of appropriate fractions gave 5.0 g of brown oil.

(B) 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl>-1-piperidinyl]propoxy]-3-dimethylaminophenyl] ethanone

A mixture of 1-[4-(3-chloropropoxy)-3-dimethylaminophenyl]ethanone (2.9 g, 0.0113 mol), 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.5 g, 0.0113 mol), K_2CO_3 (1.7 g, 0.0122 mol), KI (200 mg) and acetonitrile (125 ml) was stirred at reflux for 18 hours. The cooled reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried with magnesium sulfate and concentrated to yield 5.3 g of an amber oil. The compound was purified by preparative HPLC (Waters Associates prep LC/System 500 utilizing 2 silica gel columns) and concentration of appropriate fractions provided 1.65 g (33%). After combining with two additional samples, the compound (3.4 g, 7.74 mmol total) was taken up in ethyl acetate and fumaric acid (0.90 g, 7.75 mmol) was added. The mixture was stirred at a mild reflux for 30 minutes and then for 1 hour at ambient temperature. The reaction was left to stand overnight and was then filtered to give 3.6 g. The compound was recrystallized twice from ethanol to provide 2.3 g and once from acetonitrile to yield 1.9 g of the compound as a fumarate salt.

The compound was converted to the free base by suspending it in dilute NaOH and extracting with dichloromethane. After washing the dichloromethane extract with water and drying with $MgSO_4$, the solvent was removed in vacuo to give 1.4 g (14%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)propoxy]-3-dimethylaminophenyl] ethanone as a beige solid, m.p.=94°–96° C.

ANALYSIS

Calculated for $C_{25}H_{30}FN_3O_3$: 68.32% C 6.88% H 9.56% N.

Found: 67.74% C 6.74% H 9.40% N.

EXAMPLE 63

1-[4-[3-[4-(6-Fluoro-1,3-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-methoxyphenyl]ethanone hydrochloride

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.4 g, 0.02 mol), 1-[4-(3-chloropropoxy)-2-methoxyphenyl]ethanone (4.8 g, 0.02 mol), K_2CO_3 (2.8), KI (200 mg) and acetonitrile (110 ml) was stirred and refluxed for 16 hours. The reaction was filtered and the filtrate concentrated to afford 9.0 g of a brown oil. The oil was taken up in acetone and fumaric acid (2.5 g, 0.022 mol) was added. The mixture was heated to reflux and then it was stirred at ambient temperature for 1 hour. The resultant fumarate salt (7.0 g) was collected and then reversed to the free base with aqueous sodium hydroxide to afford 4.6 g of a soft solid. The solid was flash chromatographed on silica gel with dichloromethane-methanol (10%) as eluent, and after concentration of the appropriate fractions afforded 3.6 g of an off-white solid. The solid was dissolved in anhydrous ether and ethereal HCl was added to precipitate 3.3 g of the hydrochloride salt. The salt was recrystallized from ethanol to afford 3.3 g of product. Occluded alcohol was removed to yield 2.8 g (29%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-methoxyphenyl]ethanone hydrochloride, m.p.=193°–195° C.

ANALYSIS

Calculated for $C_{24}H_{28}ClFN_2O_4$: 62.27% C 6.10% H 6.05% N.

Found: 61.88% C 5.90% H 5.96% N.

EXAMPLE 64

1-[4-(3-Chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone

(A) 4-(3-Chloropropoxy]-3-methoxybenzoic acid

To a stirred suspension under nitrogen of sodium hydride (6.4 g, 0.13 mol, of about 50% oil dispersion-ether washed) in tetrahydrofuran (220 ml) was added pyrazole (4.4 g, 0.06 mol) in tetrahydrofuran (60 ml), dropwise. After complete addition, the reaction was stirred for about 15 minutes, and then 4-(3-chloropropoxy)-3-methoxybenzaldehyde (24.5 g, 0.107 mol) was added. The nitrogen was stopped and air was sparged into the reactor for about 3 hours. The reaction was then allowed to stir at ambient temperature open to the atmosphere for 16 hours. Water was added, the reaction was cooled in an ice bath, and concentrated hydrochloric acid (25 ml) was added dropwise. More water was added and the yellow solid that separated was collected to afford 16.2 g of product. The filtrate was then extracted with ethyl acetate to afford an additional 9.3. The samples were combined and recrystallized from acetonitrile to yield 12.6 g of a light, yellow solid, m.p.=154°–156° C. A 4.0 g sample was recrystallized from acetonitrile to yield 2.6 g of a yellow solid. This was combined with 0.4 g from another sample and recrystallized again from acetonitrile with charcoal treatment to afford 2.0 g of 4-(3-chloropropoxy)-3-methoxy) benzoic acid as a yellow solid, m.p.=157°–159° C.

ANALYSIS

Calculated for $C_{11}H_{13}ClO_4$: 54.00% C 5.35% H.

Found: 54.65% C 5.34% H.

(B) 4-(3-Chloropropoxy)-3-methoxybenzoyl chloride

To a mixture of 4-(3-chloropropoxy)-3-methoxybenzoic acid (2.4 g, 0.01 mol) in dichloromethane (5 ml) was added thionyl chloride (0.9 ml, 0.012 mol) dissolved in dichloromethane (5 ml). The reaction was stirred and refluxed for 1 hour, and then the dichloromethane was removed in vacuo to leave a dark oil. The oil was triturated with hexane and the solid that formed while scratching with a glass rod was collected to afford 1.6 g of 4-(3-chloropropoxy)-3-methoxybenzoyl chloride, m.p.=60°–63° C.

(C) 1-[4-(3-Chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone

To a stirred mixture of 4-(3-chloropropoxy)-3-methoxybenzoyl chloride (10.0 g, 0.038 mol) in methylene chloride (55 ml) cooled to −70° C., there was condensed into a reactor bromotrifluoromethane (70 g, 0.047 mol). There was then added to the reactor hexamethylphosphoroustriamide (9.4 g, 0.041 mol) dissolved in dichloromethane (7 ml). The first 90% was added quite rapidly, and the remainder at a slower rate. After complete addition, the reaction was stirred at −70° C. to −65° C. for an additional hour. The reaction mixture was allowed to come to room temperature. An equal volume of hexane was added and the layers were separated. The lower layer was extracted with hexane and then with diethylether. The extracts were combined and concentrated to yield 5.6 g of a thick, colorless oil. The oil was chromatographed on a Waters Prep 500 LC utilizing two silica gel columns and eluting with 20% ethyl acetate-hexane. Concentration of appropriate fractions gave 2.7 g of a light oil, which after evacuation at high vacuum solidified to a waxy, white solid (2.4) of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone.

EXAMPLE 65

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylbenzene methanol

(A) 1-[4-(3-chloropropoxy-3-hydroxyphenyl] ethanone

A mixture of 1-[4-(3-chloropropoxy)-3-methoxyphenyl] ethanone (10.0 g, 0.0412 mol) and concentrated H_2SO_4 (50 ml) was stirred at 65° for 23 hours. The cooled reaction was poured into 250 g of ice and was stirred vigorously for 10 minutes. The aqueous mixture was extracted with dichloromethane (CH_2Cl_2) and the resultant dichloromethane extract was washed well with 5% sodium hydroxide. The basic phases were combined and washed with dichloromethane. The aqueous mixture was cooled in an ice bath and concentrated hydrochloric acid was added until a precipitate formed. The product was isolated by filtration and dried to yield 3.1 g of a light brown solid. This was combined with an additional sample (5.0 g total) and two consecutive recrystallizations from toluene provided 3.4 g (22%) of 1-[4-(3-chloropropoxy)-3-hydroxyphenyl] ethanone as a beige solid, m.p.=101°–103° C.

ANALYSIS

Calculated for $C_{11}H_{13}ClO_3$: 57.78% C 5.73% H.

Found: 58.17% C 5.66% H.

(B) 4-(3-chloropropoxy)-3-hydroxy-α-methylbenzene methanol

To a flask charged with sodium borohydride (1.5 g, 0.0394 mol) under nitrogen and chilled to 10° was added, slowly, a solution of 1-[4-(3-chloropropoxy)-3-hydroxyphenyl]ethanone (6.0 g, 0.0262 mol) dissolved in ethanol-tetrahydrofuran (120 ml, 2:1). After total addition, the ice bath was removed and the reaction was stirred at ambient temperature for 3 hours. An additional amount of sodium borohydride (0.2 g, 0.053 mol) was carefully added. After stirring at ambient temperature for one hour, the solvent was removed in vacuo. The resultant solid residue was diluted with water (100 ml) and left overnight. The product was isolated by vacuum filtration yielding 3.8 g. Two consecutive recrystallizations from toluene provided 3.3 g (55%) of 4-(3-chloropropoxy)-3-hydroxy-α-methylbenzene methanol as a light brown solid, m.p.= 107°–109° C.

ANALYSIS

Calculated for $C_{11}H_{15}ClO_3$: 57.27% C 6.55% H.

Found: 57.60% C 6.43% H.

(C) 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylenebenzene methanol

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.3 g, 0.0195 mol), 4-(3-chloropropoxy)-3-hydroxy-α-methylbenzenemethanol (4.5 g, 0.0195 mol), KI (200 mg), $NaHCO_3$ (1.8 g, 0.0215 mol) and CH_3CN (125 ml) was stirred at reflux under nitrogen for 24 hours. The cooled reaction was filtered and the filter cake was washed with CH_3CN. The filtrate was concentrated to afford an oily residue, which was partitioned between water and ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$, and concentrated to yield 8.6 g of a dark oil. The oil was purified by preparative HPLC (Waters Associates prep LC/system 500) to yield 5.0 g. The compound was recrystallized twice from ethanol to provide 3.9 g (49%) of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylbenzene methanol as a light beige solid, m.p.=142°–144° C.

ANALYSIS

Calculated for $C_{23}H_{27}FN_2O_4$: 66.65% C 6.57% H 6.76% N.

Found: 66.68% C 6.35% H 6.72% N.

EXAMPLE 66

2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]aniline dihydrochloride

(A) 2-(3-chloropropoxy) aniline

To a stirred suspension of sodium hydride (11.0 g, 0.23 mol of a 50% oil dispersion) in dimethylformamide (250 ml), under nitrogen, was added, dropwise, 2-aminophenol (25.0 g, 0.23 mol) dissolved in dimethylformamide (125 ml). After complete addition, the reaction was stirred at ambient temperature for 1 hour, and then it was cooled to 5° C. (ice bath). 3-Chloro-1-bromopropane (36.2 g, 0.23 mol) in dimethylformamide (50 ml) was added, dropwise, so that the temperature did not go above 8° C. The reaction was stirred for 4 hours and then permitted to stand at ambient temperature for 16 hours. The reaction was poured into water and extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and the solvent concentrated to afford 25.4 g of a reddish, dark oil. About 12.0 g of the oil was chromatographed on HPLC columns. Concentration of the largest fractions gave 5.4 g of 2-(3-chloropropoxy) aniline as an oil.

(B) 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)propoxy]aniline dihydrochloride

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.8 g, 0.022 mol), 2-(3-chloropropoxy) aniline (4.0 g, 0,022 mol), K_2CO_3 (4.1 g, 0,022 mol), KI (0.2 g), and acetonitrile (100 ml) was stirred and refluxed for 10 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford 9.0 g of a red solid. The solid was triturated with diethyl ether to yield 3.0 g of a beige solid. This sample was combined with a sample (1.1 g) from another run, and a hydrochloride salt was prepared by dissolving the free base in ethanol and then adding ethereal HCl. The resultant salt (3.5 g) was recrystallized twice from methanol-diethyl ether to afford 2.6 g (22%) of 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)propoxy] aniline dihydrochloride as a brown solid, m.p.=253°–255° C.

ANALYSIS

Calculated for $C_{21}H_{24}FN_3O_2.2HCl$: 57.02% C 5.92% H 9.50% N.

Found: 56.68% C 5.71% H 9.53% N.

EXAMPLE 67

N-[5-Acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy-]phenyl acetamide

(A) Preparation of 1-[3-acetylamino-4-(3-chloropropoxyphenyl]ethanone

A stirred mixture of 1-[3-acetylamino-4-hydroxyphenyl] ethanone (7.7 g, 0.04 mol), K_2CO_3 (5.7), 3-chloro-1-bromopropane (8.9 g, 0,056 mol) and acetone (100 ml) was refluxed for 16 h. The reaction was allowed to cool to ambient temperature and filtered. Concentration of the filtrate yielded 8.5 g of a white solid. The solid was recrystallized from toluene and then from ethanol to afford 6.5 g of an off-white solid. A 3.3 g sample of this material was flash chromatographed on silica gel with ethyl acetate as eluent. Concentration of the appropriate fractions afforded 2.8 g of a solid. The solid was recrystallized from toluene and then from ethanol-water to yield 2.2 g (51%) of a solid, m.p.=124°–126° C.

ANALYSIS

Calculated for $C_{13}H_{16}ClNO_3$: 57.89% C 5.98% H 5.19% N.

Found: 57.08% C 5.85% H 5.13% N.

(B) N-[5-acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.4 g, 0.02 mol), 1-[3-acetylamino-4-(3chloropropoxy)phenyl]ethanone (5.5 g, 0.0205 mol), K_2CO_3(2.8 g), and acetonitrile (70 ml) was stirred and refluxed for 16 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate.

The extract was washed (water), dried ($MgSO_4$), and then it was concentrated to afford9.5 g of a brown oil. The oil was taken up in ethyl acetate and ethereal HCl was added until the reaction was acidic. The crude, brown, hydrochloride salt, was collected (8.4 g), and was immediately converted to the free base with NH_4OH, to afford 5.4 g of the compound as a brown oil. The oil was chromatographed on a Waters Preparative HPLC utilizing silica gel columns Concentration of the appropriate fractions yielded 3.5 g of N-[5-acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide as a white solid, m.p.=108°–110° C.

ANALYSIS

Calculated for $C_{25}H_{28}FN_3O_4$: 66.21% C 6.22% H 9.27% N.

Found: 66.12% C 6.25% H 9.27% N.

EXAMPLE 68

3-[1-[3-(4-Ethyl-3-methoxyphenoxy)propyl]-4-piperidinyl]6-fluoro-1,2-benzisoxazole hydrochloride

(A) 4-ethyl-2-methoxyphenol

Acetovanillone (Aldrich, 11.0 g, 0.066 mol) was dissolved in absolute ethanol (200 ml) and added to 1.5 g of 5% palladium on carbon. A few drops of concentrated hydrochloric acid were added and the mixture hydrogenated on a shaker at 42 psi. The reaction mixture was filtered through celite, and the filtrate was concentrated to afford 10.3 g of a golden liquid. This was diluted with water, extracted with diethyl ether and the organic phase was washed with water and sodium bicarbonate. The solvent was dried ($MgSO_4$) and concentrated to afford 9.3 g of a slightly yellow liquid.

(B) 4-ethyl-2-methoxy-4-(3-chloropropoxy)benzene

A mixture of 4-ethyl-2-methoxyphenyl (9.0 g, 0.059 mol), 3-chloro-1-bromopropane (13.0 g, 0.083 mol), K_2CO_3 (6.2 g) and acetone (200 ml) was stirred and refluxed for 16 hours. The reaction was allowed to cool, and then it was filtered. The filtrate was concentrated to a clear liquid. The liquid was diluted with dilute aqueous NaOH, and the basic mixture was extracted with diethyl ether. The diethyl ether was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford 11.9 g of a golden liquid. The liquid was flash chromatographed. This gave a colorless liquid, 9.9 g of 4-ethyl-2-methoxy-4-(3-chloropropoxy)benzene.

(C) 3-[1-[3-(4-ethyl-2-methoxyphenoxy)propyl]-4-piperidinyl-6-fluoro-1,2-benzisoxazole hydrochloride

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.0 g, 0.018 mol), KI (0.4), K_2CO_3 (2.5), 4-ethyl-2-methoxy-4-(3-chloropropoxy)benzene (4.4 g, 0.018 mol) and acetonitrile was refluxed for 8 hours. The reaction was poured into water, and the aqueous suspension was extracted with ethyl acetate. The ethyl acetate extract was washed (water) dried ($MgSO_4$) and the solvent concentrated to afford 7.0 g of a brown oil. The oil was combined with 2.0 g from another sample, and the combined sample was flash chromatographed on silica gel. Concentration of the appropriate fractions yielded 4.4 g of a thick oil, which solidified on standing. The solid was dissolved in ethyl acetate and ethereal HCl was added to precipitate 4.5 g of a white hydrochloride salt. Recrystallization from acetone afforded 3.0 g (29%) of 3-[1-[3-(4-ethyl-2-methoxyphenoxy)propyl-]4-piperidinyl-6-fluoro-1,2-benzisoxazole hydrochloride as a white solid, m.p.= 150°–152° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_2O_3$.HCl: 64.21% C 6.74% H 6.24% N.

Found: 64.38% C 6.84% H 6.14% N.

EXAMPLE 69

1-[3,5-Dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl] ethanone

(A) 3,5-dimethoxy-4-(3-bromopropoxy) acetophenone

To 3,5-dimethoxy-4-hydroxyacetophenone (5.2) in dimethylformamide (50 ml) at 0° C. under nitrogen, was added sodium hydride (700 mg, 1.1 eq, 98%). The resulting mixture was stirred for ten minutes until evolution of gas ceased. Potassium carbonate (4 g) was added, and then 1,3-dibromopropane was added. The mixture was heated at 60° C. for one hour. When the reaction was complete, the mixture was poured into a water/ice mixture and the resulting solution was extracted with ethyl acetate (600 ml). The ethyl acetate was washed with water, brine, and then concentrated to an oil (9 g). The product was purified by chromatography on silica gel to yield 3,5-dimethoxy-4-(3-bromopropoxy)acetophenone as a liquid oil, 7.6 g.

(B) 1-[3,5-dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl] ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 moles), K_2CO_3 (2.1 g, 15 mmoles), and 3,5-dimethoxy-4-(3-bromopropoxy) acetophenone (4.4 g, 13.8 moles) in acetonitrile (50 ml) was heated at reflux for 3 hr. At the end of the reaction, the mixture was diluted with dichloromethane (200 ml). The insolubles were filtered. The solution was concentrated to an oil (~10). The purification was done by flash chromatography on a silica gel column. The product was obtained as a colorless oil (3.85 g, 61%), which crystallized from ethanol (400 ml) to give 2.94 g of 1-[3,5-dimethoxy-4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl)-1-piperidinyl]propoxy] phenyl]ethanone as off-white crystals, m.p.=107°–108° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_5$: 65.78% C 6.40% H 6.14% N.

Found: 65.84% C 6.44% H 6.15% N.

EXAMPLE 70

N-[3-[3-[4-(6-Fluoro-1,2benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide hemifumarate

(A) 3-(3-acetamidophenoxy)propyl bromide

To 3-acetamidophenol (15.1 g) in dichloromethane (500 ml, dry) was added potassium carbonate (20 g) and then 1,3-dibromopropane (30 g). The resulting mixture was heated at reflux for 6 hours and then overnight at room temperature. After an additional 24 hours, the reaction was complete. Solids were filtered from the reaction mixture, and the solution was concentrated to an oil, which was purified to yield 3-(3-acetamidophenoxy)propyl bromide, 13.2 g.

(B) N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide hemifumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazol (9.25 g, 42 moles), K_2CO_3 (8 g, 58 moles) and 3-(3-acetamidophenoxy)propyl bromide (11.4 g, 42 mmoles) in acetonitrile (350 ml) was heated at reflux for 3 hours. At the end of the reaction, the reaction was cooled, filtered and the solids washed with dichloromethane (100 ml). The organic solvent was removed on a rotary evaporator to leave a crude oil (^{18} 18 g). Purification was by flash chromatography on a silica gel column. The product thus purified was an oil, 12.2 g, 70%. Analytically pure sample was prepared by dissolving 3 g of free base in ethanol and treating with fumaric acid solution in ethanol (850 mg:5 ml). The N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide hemifumarate crystals obtained weighed 2.73 g, m.p.=184°–186° C.

ANALYSIS

Calculated for $C_{23}H_{26}FN_3O_2.0.5C_4H_4O_4$: 63.95% C 6.01% H 8.94% N.

Found: 63.47% C 5.94% H 8.78% N.

EXAMPLE 71

3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]aniline

A stirred mixture of N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxyl]phenyl] acetamide (9.2 g, 22 moles), prepared as described in the previous example, in 15% hydrochloric acid (110 ml) was heated at 100° C. for 2.5 hours until a homogeneous solution resulted. The reaction was cooled to 0° C. in an ice bath and basified with 50% NaOH. The product was extracted with ethyl acetate (3x200 ml). The ethyl acetate solution was washed with water, brine, then dried over Na_2SO_4. The solvent was removed. The crude product was purified on a flash chromatography column. The product thus obtained was a solid: 6.6 g (80%). Recrystallization from hot ethanol (50 ml) gave 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]aniline as off-white crystals: 3.46 g, m.p.=115°–117° C.

ANALYSIS

Calculated for $C_{21}H_{24}FN_3O_2$: 68.27% C 6.55% H 11.37% N.

Found: 68.34% C 6.53% H 11.31% N.

EXAMPLE 72

3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyaniline

A mixture of 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenylacetamide (4.2 g, 9.5 mmoles), prepared as in Example 26 above, in 15% hydrochloric acid (60 ml) was heated at reflux (~110° C.) for 2 hours. At the end of the reaction, the solution was cooled to 0° C. then basified with 25% NaOH to pH of 10. The product was extracted into ethyl acetate (300 ml). The ethyl acetate solution was washed with water and brine, then dried over Na_2SO_4. The solvent was removed at reduced pressure. The crude oil was purified by flash chromatography on a silica gel column. The product thus purified was an oil, 2.6 g. Crystallization from ethanol (5 ml) and petroleum ether (3 ml) yielded 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyaniline as fine crystals: 1.2 g; m.p.=94°–95° C.

ANALYSIS

Calculated for $C_{22}H_{26}FN_3O_3$: 66.15% C 6.56% H 10.52% N.

Found: 66.16% C 6.54% H 10.44% N.

EXAMPLE 73

1-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methylaminophenyl] ethanone fumarate

(A) 1-[(3-N-acetyl-N-methylamino)-4-hydroxyphenyl]ethanone

A solution of 2-methoxy(methylamino)benzene (26.0 g, 0.19 mol) and 1,2-dichloroethane was cooled to 10°–15° and a solution of acetyl chloride (33.8 g, 0.43 mol) dissolved in dichloroethane (50 ml) was dripped in slowly. Following this addition, an additional 100 ml dichloroethane was added. The reaction was cooled to 0° and aluminum chloride (72.3 g, 0.54 mol) was added over the course of 45 minutes so that the temperature did not exceed 10°. After complete addition, the reaction was heated to reflux and was stirred for 18 hours under nitrogen. The reaction was cooled and was poured into ice. The resulting aqueous phase was extracted further with dichloromethane and the combined extracts were washed with H_2O, dried with $MgSO_4$, and concentrated to yield 32.0 g of 1-[(3-N-acetyl-N-methylamino)-4-hydroxyphenyl]ethanone as a brown solid, m.p.=168°–171° C.

(B) 1-(4-hydroxy-3-methylaminophenyl]ethanone

A mixture of 1-((3-N-acetyl-N-methylamino)-4-hydroxyphenyl]ethanone (15.0 g, 0.0724 mol) and concentrated HCl (150 ml) was stirred at reflux for 3 hours. The heat was terminated and the reaction stood overnight. The reaction mixture was transferred to a 1 l beaker and was chilled in an ice-salt bath. Solid sodium bicarbonate was added cautiously until the pH was about 2, and the aqueous mixture was allowed to stand overnight. The reaction mixture was continued to be made basic by the addition of solid sodium bicarbonate. After pH 8 was achieved, the reaction mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with a 200 ml aliquot of water and this was then fed through a bed of celite. After washing the cake with fresh ethyl acetate the phases were separated. The ethyl acetate extract was washed several more times with water, dried with $MgSO_4$ and concentrated to yield 10.5 g of a dark solid of 1-(4-hydroxy-3-methylaminophenyl)ethanone.

(C) 1-[4-(3-chloropropoxy)-3-methylaminophenyl] ethanone

To a stirred suspension of sodium hydride (0.87 g, 0.0182 mol of a 50% oil dispersion) in dimethylformamide (25 ml) under nitrogen and cooled to 0° in an ice-salt bath was added, dropwise, a solution of 1-(4-hydroxy-3-methylaminophenyl)ethanone (3.0 g, 0.0182 mol) dissolved in dimethylformamide (55 ml) so that the temperature did not rise above 3°. After the addition was complete, the reaction was stirred for 80 minutes at ambient temperature. The reaction was cooled to 5° and a solution of 1-bromo-3-chloropropane (3.1 g, 0.0120 mol) in dimethylformamide (20 ml) was added dropwise. After this addition was complete, the ice bath was removed and the reaction was stirred at ambient temperature for 2.5 hours. Water (75 ml) was carefully added and after stirring vigorously for 5 minutes, the reaction was left to stand overnight. The

aqueous mixture was extracted with ethyl acetate and the ethyl acetate extract was washed with water, dried with $MgSO_4$, and concentrated to yield 3.9 g of a dark solid. The compound was purified by preparative HPLC to afford 2.4 g of a beige solid. This was combined with an additional sample (3.8 g total) and two consecutive recrystallizations from ethanol gave 2.1 g (31%) of 1-[4-(3-chloropropoxy)-3-methylaminophenyl]ethanone as a fluffy, beige solid, m.p.=115°–117° C.

ANALYSIS

Calculated for $C_{12}H_{16}C_{16}ClNO_2$: 59.63% C 6.67% H 5.79% N.

Found: 59.49% C 6.64% H 5.79% N.

(D) 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy-3-methylaminophenyl]ethanone fumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (1.9 g, 0.079 mol), 1-[4-(3-chloropropoxy)-3methylaminophenyl]ethanone (1.9 g, 0.079 mol), K_2CO_3 (1.1 g), KI (0.1 g), and acetonitrile (95 ml) was refluxed for 16 hours. The reaction was poured into water and the aqueous suspension extracted with ethyl acetate. The extract was washed (water and brine), dried ($MgSO_4$), and then the solvent was concentrated to afford 3.2 g of a thick, brown oil. The oil was chromatographed on a Waters Prep 500 LC on silica gel columns, and concentration of the appropriate fractions afforded 1.5 g of a brown oil. The oil was dissolved in acetone and fumaric acid (0.4 g, 0.003 mol) was added, and 1.9 g of a white fumaric salt was collected. The salt was recrystallized from dimethylformamide to yield 1.1 g (25%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy-3-methylaminophenyl]ethanone fumarate as a white solid, m.p.=98°–200° C.

ANALYSIS

Calculated for $C_{28}H_{32}FN_3O_6S$: 60.31% C 5.78% H 7.54% N.

Found: 60.02% C 5.88% H 7.68% N.

EXAMPLE 74

N-[3-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]acetamide

(A) N-[3-(3-chloropropoxy)-4-methoxyphenyl] acetamide

To a stirred suspension, under nitrogen, of sodium hydride (1.8 g, 0.038 mol) in dimethylformamide (60 ml) was added dropwise, N-(3-hydroxy-4-methoxy)acetamide (6.1 g, 0.034 mol) dissolved in dimethylformamide (23 ml). After complete addition, the reaction was stirred at ambient temperature for 0.5 hour, and then 3-chloro-1-bromopropane (5.2 g, 0.033 mol) in dimethylformamide (10 ml) was added, dropwise. The reaction was stirred at ambient temperature for 16 hours, and then it was poured into water, and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$) and the solvent concentrated to afford a purple solid. The solid was triturated with diethyl ether and collected to afford 2.8 g of a purple solid. This sample was combined with a sample (1.2 g) from another run and was recrystallized from toluene twice to yield 2.9 g of an off-white solid. The solid was flash chromatographed on a 200 g of silica gel, eluting the column with ethyl acetate, and subsequent concentration of the appropriate fractions afforded 2.4 g of a white solid. Recrystallized of the compound from toluene yielded 2.3 g (17%) of N-[3-(3-chloropropoxy-4-methoxyphenyl]acetamide, m.p.=112°–114° C.

ANALYSIS

Calculated for $C_{12}H_{16}ClN_3$; 55.93% C 6.26% H 5.44% N.

Found: 56.25% C 6.29% H 5.44% N.

(B) N-[3-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]acetamide

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (4.0 g, 0,017 mol), N-[3-(3-chloropropoxy)-4-methoxyphenyl]acetamide (4.3 g, 0.017 mol), K_2CO_3 (2.3 g), KI (0.2 g) and acetonitrile (200 ml) was refluxed for 10 hours. The cooled reaction mixture was filtered and the filtrate was concentrated to yield a dark oil. The oil was dissolved in acetone, and ethereal HCl was added to yield 5.7 g of a yellow hydrochloride salt. The salt was reversed to the free base and the resultant oil (5.2 g) was chromatographed on a Waters Associates Prep LC utilizing silica gel columns. Concentration of the appropriate fractions yielded 4.7 g of an oil, which was converted to a hydrochloride salt. The salt was converted to its free base yielding 2.8 g of a brown oil. The oil was stirred vigorously with ether to yield 1.4 g (18%) of N-[3-[3-[4-(6-fluoro-1,2-benzoisothiazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]acetamide as a white solid, 1.4 g, m.p.=109°–111° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_3S$: 63.00% C 6.17% H 9.18% N.

Found: 62.80% C 6.17% H 8.86% N.

EXAMPLE 75

1-[4-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrochloride

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (4.0 g, 0.017 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (4.1 g, 0,017 mol), K_2CO_3 (2.3 g), KI (0.2 g), and acetonitrile (100 ml) was refluxed for 9 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford 8.0 g of a brown oil. The oil was chromatographed on a Waters Prep 500 HPLC on silica gel columns. Concentration of the appropriate fractions afforded a gum-like residue, which upon triburation with isopropyl ether afforded 1.9 g of a white solid. The solid was dissolved in absolute ethanol, and ethereal HCl was added to precipitate 1.7 g of a hydrochloride salt. Concentration of the isopropyl ether filtrate, and similar treatment of the residue, afforded an additional 0.5 g of the salt. The samples were combined and recrystallized from absolute ethanol to yield 1.7 g (21%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrochloride as a white solid, m.p.=221°–223° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3S.HCl$: 60.18% C 5.89% H 5.85% N.

Found: 60.01% C 5.97% H 5.79% N.

EXAMPLE 76

N,N-Dimethyl-4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide

(A) N,N-dimethyl-4-bromopropoxy-3-methoxybenzamide

To N,N-dimethyl-4-hydroxy-3-methoxybenzamide (5.64 g, 28.7 mmol) in acetonitrile (450 ml) was added potassium

carbonate (7.9 g) followed by 1,3-dibromopropane (11.6 g). The resulting reaction mixture was refluxed for 3 hours and stirred at room temperature for 12 hours. The mixture was filtered and concentrated to an oil. Following purification by column chromatography, N,N-dimethyl-4-bromopropoxy-3-methoxybenzamide as a colorless oil (7.6 g) was obtained.

(B) N,N-dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzoisoxazole (3.9 g, 17.7 moles), N,N-dimethyl-4-bromopropoxy-3-methoxybenzamide (5.54 g, 17.5 mmoles) and K_2CO_3 (3 g) in acetonitrile (250 ml) was heated at reflux for one hour. At the end of the reaction, the insolubles were filtered and washed with dichloromethane. The solvent was removed on a rotary evaporator. The residue was purified by flash chromatography over a silica gel column. The product thus obtained as an oil weighted 7 . Crystallization from hot ethanol (45 ml) afforded analytically pure N,N-dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzamide, 3.95 g, 50%, as light yellow crystals, m.p.=126°–127° C.

ANALYSIS

Calculated for $C_{25}H_{30}FN_3O_4$: 65.92% C 6.64% H 9.22% N.

Found: 65.76% C 6.64% H 9.14% N.

EXAMPLE 77

1-[4-[3-[4-(6-Fluoro-1,2-benzoisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone oxime

A mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (4.3 g, 0.01 mol), prepared as in Example 3 above, hydroxylamine hydrochloride (1.3 g, 0.018 mol), ammonium acetate (1.7 g, 0.022 mol) and ethanol-H_2O was stirred and refluxed for 16 hours. The reaction was poured into water, and the mixture was cooled in an ice bath for 2 hours. The resultant, whether solid was collected, washed with water and dried to yield 4.6 g of hydrochloride salt of the oxime, m.p. 216°–218° C. The compound was dispersed in water and ammonium hydroxide was added until the suspension was decidedly basic. The basic suspension was then extracted with dichloromethane, and after washing with water, drying ($MgSO_4$), and concentrating the extract, 3.0 g of white solid melting at 168°–170° C. were harvested. The compound was recrystallized from dimethylformamide to yield 2.3 g (52%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone oxime as a white solid, m.p.=168°–170° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_4$: 65.29% C 6.39% H 9.52% N.

Found: 65.27% C 6.44% H 9.46% N.

EXAMPLE 78

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]methoxyphenyl]ethanone oxime O-methyl ether

A solution of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]methoxyphenyl]ethanone (4.3 g, 0.01 mol), prepared as in Example 3 above, methoxylamine hydrochloride (0.93 g, 0.01 mol) in pyridine (75 ml)/ethanol (75 mg) was refluxed for 16 hours. Most of the solvent was evaporated under reduced pressure, and the residue was diluted with water to precipitate 1.6 g of a white solid, m.p. 200°–201° C. The aqueous filtrate upon standing deposited another crop of white crystals, which yielded 1.2 g of a pale, yellow solid with a m.p. of 70°–72° C. The initial crop of crystals was converted to its free base with aqueous NaOH. After extractive workup with ethyl acetate, 1.2 g of the free base was obtained. The two samples were combined and recrystallized from isopropyl ether to afford 2.0 g (44%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]methoxyphenyl]ethanone oxime O-methyl ether as colorless crystals, m.p.=97°–99° C.

ANALYSIS

Calculated for $C_{25}H_{30}FN_3O_4$: 65.92% C 6.64% H 9.22% N.

Found: 65.89% C 6.86% H 9.15% N.

EXAMPLE 79

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrazone

A stirred mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (4.3 g, 0.01 mol), prepared as in Example 3 above, hydrazine (0.8 g, 0.0025 mol), and ethanol (40 ml) was refluxed for 16 hours. The cooled solution was concentrated to yield an oily residue. The residue was triturated with water and the resultant solid was collected to afford 4.2 g of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrazone as a yellow solid. The compound was recrystallized from isopropanol and then from toluene to afford 1.7 g (39%), m.p.=106°–108° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_4O_3$: 65.44% C 6.64% H 12.72% N.

Found: 65.38% C 6.55% H12.55% N.

EXAMPLE 80

6-Fluoro]-3-[1-[3-[2-methoxy-4-(1-methylethenyl) phenoxy]propyl]-4-piperidinyl]-1,2-benzisoxazole hydrochloride

A solution of butyllithium (4.7 ml of a 2.3 M solution in hexanes, 0.0107 mol) in tetrahydrofuran (65 ml) was stirred under nitrogen and cooled to −70° to an isopropyl alcohol-dry ice bath. Methyltriphenylphosphonium bromide (3.8 g, 0.0106 mol) wa added portionwise over the course of 10 minutes. After complete addition, the reaction was stirred at −65° C. for one hour and was then allowed to gradually warm up to ambient temperature, where it was stirred for an additional 3.5 hours. The reaction was cooled to 0° C., and a solution of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone prepared as in Example 3 above (4.7 g, 0.0110 mol) dissolved in tetrahydrofuran (50 ml) was added, dropwise, over the course of 30 mixtures. After the addition was complete, the reaction was stirred at ambient temperature for 19 hours. The reaction was poured into water and the aqueous mixture was extracted with diethyl ether. The diethyl ether extract was washed several times with water, dried with $MgSO_4$ and concentrated to yield 7.0 g of a light orange solid. Recrystallization from toluene-hexane provided 1.4 g of triphenylphosphine oxide and concentration of the filtrate afforded 5.5 g of a glassy, beige solid. This was combined

with an additional sample (6.5 g total) and purification by preparative HPLC (Water's Associates prep LC/System 500) gave 5.2 g of a beige solid, which remained contaminated by triphenylphosphine oxide. The compound was taken up in anhydrous ethanol (300 ml) and methanol (5 drops) and ethereal HCl was added to precipitate 4.0 g of a pale, white solid, m.p.=192°–194° C.

ANALYSIS

Calculated for $C_{25}H_{30}ClFN_2O_3$: 65.14% C 6.56% H 6.08% N.

Found: 64.95% C 6.62% H 6.04% N.

EXAMPLE 81

(E)-1-[4-[[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl] ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10 mmoles), K_2CO_3 (2 g), (E)-4-[(4-bromo-2-butenyl)oxy-3-methoxyacetophenone (4.0 g, 1.3 eq) in acetonitrile (100 ml) was heated at reflux for 2 hours. At the end of the reaction, the solvent was removed on the rotary evaporator. The residue was extracted into dichloromethane (300 ml). The insolubles were filtered off. The dichloromethane was concentrated. The crude product was purified on a flash chromatography column. The product eluted as an oil, weight 2.87 g (64%). Recrystallization from ethanol:hexane (200 ml:5 ml) gave (E)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl] oxy]-3-methoxyphenyl]ethanone as off-white crystals: 2.46 g; m.p.=91°–93° C.

ANALYSIS

Calculated for $C_{25}H_{27}FN_2O_4$: 68.48% C 6.21% H 6.39% N.

Found: 68.28% C 6.12% H 6.27% N.

EXAMPLE 82

(Z)-1-[4-[(4-Chloro-2-butenyl)oxy]-3-methoxyphenyl]ethanone

A stirred mixture of 4-hydroxy-3-methoxyacetophenone (16.6 g, 0.1 mole), K_2CO_3 (14 g, 0.10 mole) and cis-1,4-dichloro-2-butene (Aldrich, 15 g, 0.12 mole) in acetonitrile (250 ml) was heated at reflux for 2.5 hr. The mixture was filtered and concentrated to an oil. Purification was by flash chromatography. The fractions containing the purest product were combined and concentrated to give white crystals, 7.7 g, 30%. This was recrystallized from ether to give analytical pure (Z)-1-[4-[(4-chloro-2-butenyl)oxy]-3-methoxyphenyl] ethanone (2.72 g), m.p.=64°–66° C.

ANALYSIS

Calculated for $C_{13}H_{15}ClO_3$: 61.30% C 5.94% H.

Found: 61.28% C 5.94% H.

EXAMPLE 83

(Z)-1-[4-[[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl] ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10 mmoles), K_2CO_3(1.8 g, 13 mmoles) and (Z)-1-[4-[(4-chloro-2-butenyl)oxy]-3-methoxyphenyl]ethanone (3.43 g, 9.7 mmoles) in acetonitrile (100 ml) was heated at reflux for 1½ hr. At the end of the reaction, the solvent was removed and the inorganics were filtered after addition of dichloromethane (250 ml). The dichloromethane solvent was removed again. The crude oil was purified on two flash chromatography columns to give a colorless oil (2.78 g). The oil was solidified by vigorously drying on a vacuum pump. Recrystallization from ethanol (10 ml) and hexane (2 ml) gave analytically pure (Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]3-methoxyphenyl]ethanone, 1.83 g, m.p.=57°–59° C.

ANALYSIS

Calculated for $C_{25}H_{27}FN_2O_4$: 68.48% C 6.21% H 6.39% N.

Found: 68.26% C 6.18% H 6.32% N.

EXAMPLE 84

(E)-1-[3-[[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-hydroxyphenyl] ethanone hydrochloride

The mixture of (E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4benzyloxyphenyl]ethanone (5.5 g, 10.7 mmole), acetic acid (50 ml), and hydrochloric acid (6 ml) was heated at 75° C. for 2 hr. At the end of reaction, the solvent was reduced about 20 ml on a rotary evaporator. The solution was poured into ice water (350 ml) and extracted with dichloromethane (3>250 ml). The dichloromethane solution was washed with brine and dried over Na_2SO_4. A solid formed on concentration of the solvent. This was collected by filtration (3.4 g). Recrystallization from hot methanol (40 ml) gave 1.82 g of (E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-hydroxyphenyl]ethanone hydrochloride as white crystals, 37.5%, m.p.=208°–210° C.

ANALYSIS

Calculated for $C_{24}H_{25}FN_2O_4.HCl$: 62.54% C 5.69% H 6.08% N.

Found: 62.40% C 5.60% H 6.04% N.

EXAMPLE 85

(E)-1-[3-[[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-benzyloxyphenyl] ethanone

(A) (E)-3-[(4'-bromo-2'-butenyl)oxy]-4-benzyloxyacetophenone

To 4-benzyloxy-3-hydroxyacetophenone (17.6 g) in acetonitrile (200 ml) was added potassium carbonate (10 g), followed by the addition of (E)-1,4-dibromobutene (19 g). The resulting mixture was heated at reflux for 3 hours. The mixture was concentrated, extracted into dichloromethane, and the potassium salt was removed by filtration. Solvent was removed, and the resulting material was purified by flash chromatography to yield 20.5 g of (E)-3-[(4'-bromo-2'-butenyl)oxy]-4-benzyloxyacetophenone as white crystals.

(E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-benzyloxyphenyl] ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5.62 g, 25.5 mmoles), K_2CO_3 (4 g, 29 mmoles), and (E)-3-[(4-bromo-2'-butenyl)oxy]-4-benzyloxyacetophenone (10 g, 26.6 mmole) in acetonitrile (125 ml) was heated at reflux for 3.5 hr. The mixture was cooled and concentrated to a crude solid. The residue was extracted into dichloromethane (300 ml) and insolubles were filtered. The crude material form the dichloromethane solu

tion was purified on a flash chromatography column. The product thus purified weighed 8 g as a pale white solid. Recrystallization from hot ethanol gave 7.11 g of (E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4benzyloxyphenyl]ethanone as off-white crystals, m.p.=124°–125° C.

ANALYSIS

Calculated for $C_{31}H_{31}FN_2O_4$: 72.36% C 6.07% H 5.44% N.

Found: 72.23% C 6.04% H 5.04% N.

EXAMPLE 86

6-Fluoro-3-[1-[3-[(5-methoxy-1H-indol-6-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole

(A) 6-(3-Chloropropoxy]-5-methoxyindole

To a stirred suspension of sodium hydride (0.94 g, 19.6 mmol of a 50% oil dispersion) in dimethylformamide (20 ml) under nitrogen and cooled to −5° was added, dropwise, 5-methoxy-6-hydroxyindole (3.2 g, 19.6 mmol) dissolved in dimethylformamide (60 ml) so that the temperature did not exceed −2°. After complete addition, the reaction was stirred for 45 minutes at 0°. While maintaining the reaction temperature between −5° and 0°, a solution of 1-bromo-3-chloropropane (3.1 g, 19.6 mmol) dissolved in dimethylformamide (15 ml) was slowly added. The mixture was stirred at ambient temperature under nitrogen for 21 hours. The reaction was cooled in an ice bath, and water was added to destroy the excess sodium hydride, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$ and concentrated to yield 5.3 g of a dark, oily liquid. This was combined with an additional sample, for a total of 10.0 g, and purification by preparative HPLC (Waters Associates prep LC/System 500) provided 5.1 g of a brown solid. A 2.5 g sample was recrystallized from isopropyl alcohol to yield 1.1 g (30%) of 6-(3-chloropropoxy)-5-methoxyindole as beige crystals, m.p.=73°–75° C.

ANALYSIS

Calculated for $C_{12}H_{14}ClNO_2$: 60.13% C 5.89% H 5.84% N.

Found: 60.26% C 5.86% H 5.77% N.

B.

6-Fluoro-3-[1-[3-[(5-methoxy-1H-indol-6-yl]oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.5 g, 11.5 mmol), 6-(3-chloropropxy)-5-methoxyindole (2.5 g, 10.4 mmol), K_2CO_3 (1.6 g, 11.5 mmol), KI (200 mg) and acetonitrile (100 ml) was stirred at reflux under nitrogen for 40 hours. The cooled reaction was poured into water and extracted with ethyl acetate. The ethyl acetate extract was washed with water, washed with brine, dried with $MgSO_4$ and concentrated to yield 4.0 g of a solid. The compound was recrystallized from ethanol to afford 3.3 g. Another recrystallization from ethanol (utilizing a charcoal treatment) provided 2.9 g (66%) of 6-fluoro-3-[1-[3-[(5-methoxy-1H-indol-6-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole as a beige solid, m.p.=156°–158° C.

ANALYSIS

Calculated for $C_{24}H_{26}FN_3O_3$: 68.07% C 6.19% H 9.92% N.

Found: 67.89% C 6.07% H 9.91% N.

EXAMPLE 87

6-Fluoro-3-[1-[3-[(1H-indol-7-yl)oxy]phenyl]-4-piperidinyl]-1,2-benzisoxazole hemifumarate

(A) 7-(3-Chloropropoxy)indole

To a stirred suspension of sodium hydride (0.8 g, 0.017 mmol of a 50% oil dispersion) in dimethylformamide (20 ml), under nitrogen, was added dropwise 7-hydroxyindole (2.1 g, 0.0157 mol) in dimethylformamide (20 ml). After complete addition, the reaction was stirred at ambient temperature for 0.5 hour and then cooled to 15° C. To this cooled solution was added, dropwise, 1-bromo-3-chloropropane (2.5 g, 0.0157 mol) in dimethylformamide (5 ml). The reaction was then stirred at ambient temperature for 16 hours. The reaction was poured into water, and the aqueous suspension extracted with ethyl acetate. The ethyl acetate was washed with water, dried ($MgSO_4$), and the solvent was concentrated to afford a dark brown oil. Following flash chromatography on silica gel, 7-(3-chloropropoxy)indole was obtained as a colorless oil, 1.0 g.

ANALYSIS

Calculated for $C_{11}H_{12}ClNO$: 63.01% C 5.77% H 6.68% N.

Found: 63.25% C 5.61% H 6.65% N.

(B) 6-Fluoro-3-[1-[3-[(1H-indol-7-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxaole hemifumarate

A stirred mixture of 7-(3-chloropropoxy)-1H-indole (3.5 g, 0.017 mol), 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.5 g, 0.017 mol), K_2CO_3 (2.3 g) and acetonitrile (60 ml) was refluxed for 11 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed with water, dried ($MgSO_4$), and the solvent was concentrated to afford a dark oil. The oil was flash chromatographed on silica gel. Upon concentration of the appropriate fractions, 3.0 g of white, foamy substance was obtained. The substance was dissolved in ethyl acetate (75 ml) and fumaric acid (0.97 g, 0.083 mol) was added. The mixture was briefly heated to reflux, and then stirred at ambient temperature for 1.5 hours. The resultant insoluble white fumaric salt was collected and afforded 4.2 g of product. Recrystallization of the salt from dimethylformamide yielded 3.1 g (36%) of 6-fluoro-3-[3-[(1H-indol-7-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole hemifumarate as a white solid, m.p.=213°–215° C.

ANALYSIS

Calculated for $C_{25}H_{26}FN_3O_4$: 66.50% C 5.80% H 9.31% N.

Found: 66.23% C 6.14% H 9.39% H.

EXAMPLE 88

6-Fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (10.0 g, 0.045 mol), K_2CO_3 (10.0 g), 3-bromo-1-propanol (7.3 g, 0,046 mol) and acetonitrile (200 ml) was refluxed for 3 hours. The reaction was poured into H_2O and 7.1 g of a beige solid was collected. The filtrate was extracted with dichloromethane, and after concentration an additional 6.7 g of crude solid was harvested. The solids were combined and triturated with refluxing ethyl acetate to afford 8.0 g of 6-fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole as an off-white solid. A sample (4.0 g) was recrystallized from ethanol-water (with charcoal treatment) to yield 2.4 g (40%) of the alcohol as a white solid, m.p.=140°–142° C.

ANALYSIS

Calculated for $C_{15}H_{19}FN_2O_2$: 64.73% C 6.88% H 10.06% N.

Found: 64.79% C 6.97% H 10.03% N.

EXAMPLE 89

6-Fluoro-3-[1-(2-pyrimidinoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate

To a stirred suspension of 6-fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole (3.6 g,

0.013 mol) in tetrahydrofuran (50 ml) was added dropwise, potassium bistrimethylsilylamide (2.6 g, 0.013 mol) dissolved in tetrahydrofuran (20 ml). After complete addition, the reaction was stirred at ambient temperature for 5 min, and then 2-chloropyrimidine (1.6 g, 0.014 mol) was added. The reaction was stirred at ambient temperature for 4 hours, and TLC at this time indicated an incomplete reaction. An additional quantity of the base (0.5 g) was added, and the reaction was allowed to proceed at ambient temperature for 14 additional hours. The reaction was poured into water and the aqueous mixture was extracted with dichloromethane. The extract was washed (H_2O), dried (K_2CO_3), and the solvent was concentrated to afford a wet solid. The solid was triturated with diethyl ether and the product that separated was collected to yield 1.0 g of the starting alcohol. The filtrate was then concentrated to afford 3.8 g of a waxy, yellow solid. This material was combined with 2.6 g from another run and the combined sample flash chromatographed on silica gel, eluting first with ethyl acetate and then with 8% diethylamine-ethyl acetate. Concentration of the appropriate fractions afforded 3.0 g of the desired compound as a yellow solid. The solid was converted to a fumarate salt with fumaric acid in acetone, and then reversed to its free base. It was combined with another sample and the combined sample (3.8 g) chromatographed on silica gel on HPLC (4.5% methanoldichloromethane as eluent). Concentration of the appropriate fractions yielded 1.6 g of a yellow solid. A fumarate salt was prepared to yield 2.1 g (16%) of 6-fluoro-3-[1-[(2-pyrimidinoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate, m.p.=184°–186° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_4O_6$: 58.47% C 5.33% H 11.86% N.

Found: 58.52% C 5.34% H 11.80% N.

EXAMPLE 90

6-Aceto-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan

(A) 6-aceto-2-mesyloxymethyl-1,4-benzodioxan

6-Aceto-2-hydroxyethyl-1,4-benzodioxan (3.39 g, 16.3 mmol) was dissolved in trichloromethane (100 ml). Triethylamine (2.5 g) was added to methylchloride (2.5 g, 1.35 eq) at 0° C. The mixture was stirred for 2 hours at room temperature. The mixture was then diluted, washed with an ice/dilute hydrochloric acid mixture (150 ml), washed with sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated to yield 5.6. Following chromatography on a SiO_2 column, 3.64 g (78% yield) of 6-aceto-2-methoxymethyl-1,4-benzodioxan were obtained.

(B) 6-aceto-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 mmoles), K_2CO_3 (2 g, 14.5 mmoles) and 6-aceto-2-mesyloxymethyl-1,4-benzodioxan (3.5 g, 12 mmoles) in acetonitrile (100 ml) was heated at reflux for 3 hr. At the end of the reaction the solvent was removed on a rotary evaporator. The residue was extracted into dichloromethane (350 ml) and the insolubles were filtered off. The dichloromethane solution was concentrated and the crude oil was purified by flash chromatography. The product thus obtained weighed 3.38 g (59%). Recrystallization from ethanol gave 6-aceto-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan as light yellow crystals (3.2 g), m.p.=122°–123° C.

ANALYSIS

Calculated for $C_{23}H_{23}FN_2O_4$: 67.31% C 5.65% H 6.83% N.

Found: 67.24% C 5.50% H 6.75% N.

EXAMPLE 91

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] methyl-1,4-benzodioxan

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 mmoles), K_2CO_3 (2.45 g, 17.7 mmoles), 2-methanesulfonyloxymethyl-1,4-benzodioxan (3.35 g, 13.7 mmole) in acetonitrile (100 ml) was heated at reflux for 12 hours. At the end of the reaction, the insolubles were filtered and rinsed with dichloromethane. The organic solution was concentrated. The crude oil was purified by flash chromatography on a silica gel column. The fractions containing the pure product were pooled and concentrated to a light yellow oil (3.94: g, 74%). Crystallization from ethanol and petroleum ether gave 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan as off-white crystals, 2.22 g, m.p.=86°–87° C.

ANALYSIS

Calculated for $C_{21}H_{21}FN_2O_3$: 68.47% C 5.75% H 7.60% N.

Found: 68.33% C 5.75% H 7.51% N.

EXAMPLE 92

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-1,4-benzodioxan

(A) 2-mesyloxyethyl-1,4-benzodioxan

To the compound 2-hydroxymethyl-1,4-benzodioxan (11.96 g) in dichloromethane (450 ml) was added triethylamine (0.12 mol, 10 ml). Mesylchloride (9.2 g) was then added dropwise and the reaction mixture was stirred for one hour at room temperature. After completion of the reaction, the solution was washed with water, brine, and concentrated to an oil, which was purified by chromatography on silica gel to yield 2-mesyloxyethyl-1,4-benzodioxan, 17.08 g.

(B) 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,4-benzodioxan

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.7 g, 21 moles), K_2CO_3 (3.5 g, 25.4 moles) and 2-mesyloxyethyl-1,4-benzodioxan (5.5 g, 21.3 mmoles) in acetonitrile (250 ml) was heated at reflux for 3.5 hours. At the end of the reaction, insolubles were filtered. The solid was washed with dichloromethane (200 ml). The solutions were combined and evaporated to an oil. This crude oil was purified by flash chromatography on a silica gel column. The material thus obtained was crystallized from ethanol. The 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,4-benzodioxan crystals were collected and weighed 3.8 g, 48%, m.p.=112°–113° C.

ANALYSIS

Calculated for $C_{22}H_{23}FN_2O_3$: 69.09% C 6.06% H 7.32% N.

Found: 69.17% C 6.02% H 7.31% N.

EXAMPLE 93

6-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-7-methoxy-1-tetralone

(A) 6-(3-chloropropoxy)-1-tetralone

A mixture of 6-hydroxy-7-methoxy-1-tetralone (J. Org. Chem., 1985, 50, 4937) (1.5 g, 7.8 mmol), K_2CO_3 (1.7 g,

12.3 mmol), and acetone (30 ml) was stirred at reflux under nitrogen for 45 minutes. The reaction was cooled to ambient temperature and a solution of 1-bromo-3-chloropropane (1.9 g, 12.1 mmol) dissolved in 8 ml acetone was dripped into the mixture. After total addition, the reaction was heated to reflux and stirred under nitrogen for 21 hours. The reaction was cooled to ambient temperature and filtered. The filter cake was washed well with acetone and the filtrate was concentrated to yield 2.0 g 6-(3-chloropropoxy)-7-methoxy-1-tetralone as an amber oil.

(B) 6-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-7-methoxy-1-tetralone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (0.78 g, 3.6 mmol), K_2CO_3 (0.60 g, 4.1 mmol), KI (100 mg), 6-(3-chloropropoxy)-7-methoxy-1-tetralone (0.87 g, 3.2 mmol), and acetonitrile (50 ml) was stirred at reflux under nitrogen for 17 hours. The cooled reaction was poured into 100 ml of water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried with $MgSO_4$ and concentrated to yield 1.7 g of a brown oil. The oil was purified by preparative HPLC (Waters Associates Prep LC/system 500) to afford 1.0 of a light brown solid. This was combined with an additional sample (2.3 g total) and recrystallization from ethanol yielded 1.7 g. A subsequent recrystallization from ethanol gave 1.25 g (36%) of 6-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-7-methoxy-1-tetralone as a beige powder, m.p.=129°–131° C.

ANALYSIS

Calculated for $C_{26}H_{29}FN_2O_4$: 69.01% C 6.46% H 6.19% N.

Found: 68.77% C 6.43% H 6.16% N.

EXAMPLE 94

N-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]-6-acetyl-2-benzoxazolinone

(A) N-(3-chloropropyl)-2-benzoxazolinone

To a stirred suspension of sodium hydride (7.8 g, 0.16 mol, ether-washed) in dimethylformamide (75 ml) was added dropwise under nitrogen, 2-benzoxazolinone (20.0 g, 0.15 mol) dissolved in dimethylformamide (150 ml). After complete addition the reaction was stirred at ambient temperature for 30 min, and then it was cooled to −5° C. with an ice-acetone bath. A solution of 3-chloro-1-bromopropane (46.6 g, 0.30 mol) in dimethylformamide (50 ml) was added dropwise (temperature never exceeded 0° C.). The reaction was allowed to reach ambient temperature and was stirred for 16 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed with water, dried ($MgSO_4$), and the extract concentrated to afford 21.9 of a brown solid. The solid was recrystallized from toluene-hexane to afford N-(3-chloropropyl)-2-benzoxazolinone as large needles, 15.6 g, m.p.=264°–266° C.

(B) N-(3-chloropropyl)-6-acetyl-2-benzoxazolinone

A mixture of N-(3-chloropropyl)-2-benzoxazolinone (8.5 g, 0.04 mol), polyphosphoric acid (100 g), and acetic acid (2.4 g, 2.3 ml, 0.04 mol), was stirred and heated at 100° C. for 2 hours. The hot solution was poured into ice-water to deposit a yellow gum. The mixture was extracted with dichloromethane, and insolubles were filtered. The dichloromethane extract was washed with water, dried (K_2CO_3), and concentrated to afford 6.4 g of a slightly green solid. This was recrystallized from ethanol (95%) to yield N-(3-chloropropyl)-6-acetyl-2-benzoxazolinone as a brown solid, 3.5 g, m.p.=100°–103° C.

(C) N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]-6-acetyl-2-benzoxazolinone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.0 g, 0.009 mol), N-(3-chloropropyl)-6-acetyl-2-benzoxazolinone (2.4 g, 0.009 mol), K_2CO_3 (3.6 g), a few crystals of KI, and acetonitrile (50 ml) was stirred and refluxed for 13 hours. The reaction was poured into water, and a dark, brown solid that separated was collected to afford 3.3 g of crude product. The solid was chromatographed on a Waters Prep 500 HPLC. Concentration of appropriate fractions afforded 2.3 g of a yellow solid, and recrystallization from ethyl acetate yielded 1.2 g (31%) of N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]-6-acetyl-2-benzoxazolinone, m.p.=152°–154° C.

ANALYSIS

Calculated for $C_{24}H_{24}FN_3O_4$: 65.89% C 5.53% H 9.61% N.

Found: 65.67% C 5.48% H 9.52% N.

EXAMPLE 95

N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]phthalimide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (6.44 g, 29.1 mmole), K_2CO_3 (6.4 g, 46 mmoles), N-(3-bromopropyl)phthalimide (8.4 g, 31 mmoles) in acetonitrile (150 ml) was heated at reflux for 3.5 hr. The insolubles were filtered. The solvent was removed at reduced pressure and the residue was purified by silica gel column chromatography to give N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]phthalimide as a white solid. Recrystallization from ethanol yielded 9.8 g (83%) of off-white crystals, m.p.=129°–1300C.

ANALYSIS

Calculated for $C_{23}H_{22}FN_3O_3$: 67.89% C 5.44% H 10.31% N.

Found: 67.49% C 5.38% H 10.13% N.

EXAMPLE 96

1-(3-Aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)-piperidine dihydrochloride

A mixture of N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]phthalimide (8.5 g, 21 moles), hydrazine monohydrate (1.5 g, 30 mmoles) in methanol (60 ml) was heated at reflux for 2 hours. At the end of the reaction, methanol was removed to leave a crude solid. To this was added water (60 ml), then the mixture was acidified with HCl to pH 1. The insolubles were filtered with the aid of a pad of celite. The aqueous solution was basified with 50% NaOH, (pH 13), then extracted with dichloromethane. The combined dichloromethane solution was washed with brine, then dried to a colorless oil (4.5 g). The analytical sample (1.5 g) was prepared by treating the oil with HCl in ethanol at 0° C. The 1-(3-aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride was obtained as white crystals, 2.03 g, m.p.=231°–234° C.

ANALYSIS

Calculated for $C_{15}H_{20}FN_3O.2HCl$: 51.44% C 6.33% H 12.00% N.

Found: 51.35% C 6.49% H 11.90% N.

EXAMPLE 97

cis-2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]-hexahydro-1H-isoindole-1,3-dione hydrochloride

A mixture of 1-(3-aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (3.01 g, 10.8 moles) and cis-1,2-cyclohexane-dicarboxylic anhydride (1.9 g, 12.3 mmoles) in dry pyridine (30 ml) was heated at reflux for 16 hours. The dark brown solution was concentrated to dryness on a rotary evaporator. The crude residue was purified twice by flash chromatography over a silica gel column. The pure product thus obtained weighed 2.5 g (67%). This was converted to the hydrochloride salt by treatment with HCl in ethanol (50 ml). The cis-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]hexahydro-1H-isoindole-1,3-dione hydrochloride crystals so obtained weighed 3.0 g. m.p.=242°–245° C.

ANALYSIS

Calculated for $C_{23}H_{28}FN_3O_3.HCl$: 61.14% C 6.50% H 9.34% N.

Found: 61.32% C 6.32% H 9.27% N.

EXAMPLE 98

N-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl]phthalimide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5.5 g, 25 mole), 4-bromobutylphthalimide (8.0 g, 28.3 moles, 1.13 eq), K_2CO_3 (4.55 g, 32 mmoles) in acetonitrile (100 ml) was heated at reflux for 3 hr. At the end of the reaction, the mixture was filtered. The insolubles were washed with dichloromethane (200 ml). The organic solution was concentrated gradually to allow crystallization. The crude crystals (5.9 g) were collected. The mother liquor was concentrated to a solid (5.5 g). Purification was by flash chromatography over a silica gel column. The product (3.8 g) thus purified was recrystallized from ethanol (70 ml) to give 2.48 g of N-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl]phthalimide as white crystals, m.p.=144°–146° C.

ANALYSIS

Calculated for $C_{24}H_{24}FN_3O_3$: 68.39% C 5.74% H 9.97% N.

Found: 68.34% C 5.74% H 9.84% N.

EXAMPLE 99

1-(4-Aminobutyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride

A mixture of N-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidinyl]butyl]phthalimide (6.9 g, 16.4 mmoles) and hydrazine monohydrate <1.64 g, 32.8 mmoles) in methanol (70 ml) was heated at reflux for 3 hours. At the end of the reaction, methanol was removed to leave a crude solid. This was dissolved in water and acidified with HCl to pH 2. The insolubles were filtered. The aqueous solution was basified with 50% NaOH, and then extracted with dichloromethane. The dichloromethane solution was washed with water and brine, and then dried over $MgSO_4$. The solvent was removed to a colorless oil: 4.48. This oil was treated with 2.5 equivalents of HCl in ethanol. The solid was collected. Recrystallization from ethanol (65 ml) and methanol (20 ml) gave 2.0 of 1-(4-aminobutyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride as white crystals, m.p.=234°–237° C.

ANALYSIS

Calculated for $C_{16}H_{22}FN_3O.2HCl$: 52.75% C 6.64% H 11.53% N.

Found: 52.37% C 6.59% H 11.07% N.

EXAMPLE 100

cis-2-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl]-hexahydro-1H-isoindole-1,3-dione hydrochloride

A mixture of 1-(4-aminobutyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (4.7 g, 16.1 mmoles) and cis-1,2-cyclohexanedicarboxylic anhydride (3.23 g, 21 mmoles) in pyridine (45 ml) was heated at reflux for 8 hours. At the end of the reaction, pyridine was removed to dryness. The crude product was purified on a silica gel column. The material thus obtained weighed 3.18 g (45%) as a clear oil. This oil was dissolved in ethanol (15 ml), then was treated with HCl in ethanol (45 ml). Crystallization took place upon cooling. The crystals were collected, 3.2 g, m.p.=229°–231° C.

ANALYSIS

Calculated for $C_{24}H_{30}FN_3O_3.HCl$: 62.13% C 6.73% H 9.06% N.

Found: 61.79% C 6.68% H 8.92% N.

EXAMPLE 101

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]thio]-3-methoxyphenyl]ethanone

(A) 1-[4-[(3-chloropropyl)thio]-3-methoxyphenyl] ethanone

A mixture of 1-(4-thio-3-methoxyphenyl)ethanone (10.0 g, 0.0549 mol), potassium carbonate (9.0 g, 0.0651 mol), and acetone (100 ml) was stirred at reflux under nitrogen for 30 minutes. The reaction was cooled to ambient temperature and a solution of 1-bromo-3-chloropropane (6.5 ml, 9.5 g, 0.0604 mol) dissolved in acetone (25 ml) was dripped into the reaction. After complete addition, the reaction was heated to reflux and stirred under nitrogen for 17 hours. After the reaction was carried to substantial completion, the reaction mixture was filtered and the resulting filter cake was washed with acetone. The filtrate was concentrated to provide an amber oil. A small sample was solidified by trituration with hot cyclohexane to provide 1-[4-[(3-chloropropyl)thio]-3-methoxyphenyl]ethanone as a yellow solid, 11.7 g, m.p. 53°–55° C.

(B) 1-[4-[[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]thio]-3-methoxyphenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazol (3.0 g, 0.0136 mol), 1-[4-[(3-chloropropyl)thio]-3-methoxyphenyl]ethanone (3.5 g, 0.0136 mol), K_2CO_3 (2.3 g, 0.0166 mol), KI (200 mg) and CH_3CN (100 ml) was stirred at reflux under nitrogen for 7.5 hours and then was left at ambient temperature for 65 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed twice with water, once with brine and dried over $MgSO_4$. The solvent was removed in vacuo to afford 6.8 g of a light brown oil. The sample was purified by flash chromatography. Concentration of appropriate fractions yielded 3.0 g. Recrystallization from ethanol provided 2.4 g (41%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propyl]thio]-3-methoxyphenyl]ethanone as a beige solid, m.p.=93°–95° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3S$: 65.14% C 6.15% H 6.33% N.

Found: 64.66% C 6.17% H 6.26% N.

EXAMPLE 102

4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-[4-(2'-methoxyphenyl)]butylpiperidine maleate

(A) 2-(4-bromobutyl]anisole

2-Bromoanisole (2.0 g, 1.07 mmol) in tetrahydrofuran (20 ml) was cooled to −78° C. under nitrogen and secondary butyllithium (1.3M, 10 ml, 1.3 eq) was charged into the resulting solution for two hours. The solution was quenched with 1,4-dibromobutane (3.2 g) and allowed to stir at ambient temperature overnight. The mixture was diluted with ethyl acetate, washed with water and brine, and concentrated to an oil. Following chromatography on a SiO_2 column, 2.4 g of 2-(4-bromobutyl)anisole were obtained.

(B) 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2-methoxyphenyl]butylpiperidine maleate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.36 g, 10.7 mole), K_2CO_3 (2 g, 14.5 mmoles) and 2-(4-bromobutyl)anisole (2.4 g, 10 moles) in acetonitrile (100 ml) was heated at reflux for 2.5 hr. At the end of reaction, the solvent was removed. The residue was extracted into dichloromethane (200 ml) and filtered. The dichloromethane solution was concentrated. The crude oil obtained was purified on a flash chromatography column. The material thus purified was a light yellow oil (2.73 g, 53%). This oil was dissolved in ethanol and treated with maleic acid (607 mg, 1.0 eq) in ethanol. The 4-(6-fluoro-1, 2-benzisoxazol-3-yl)-1-(2'-methoxyphenyl)butylpiperidine maleate crystals formed on concentration and subsequent cooling to 0° C. These were collected and dried to yield 2.05 g, m.p.=132°–133° C.

ANALYSIS

Calculated for $C_{23}H_{27}FN_2O_2.C_4H_4O_4$: 65.05% C 6.27% H 5.62% N.

Found: 65.25% C 6.30% H 5.70% N.

EXAMPLE 103

1-[4-[4-[1-(1,3-Dithian-2-yl)ethyl]phenyl]butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine

(A) 4-bromo-1-[1,3-dithian-2-yl)ethylbenzene

To the compound p-bromoacetophenone (36.85 g, 0.185 mol) in trichloromethane (300 ml) was added 1,3-propanedithiol (25 g, 0.23 mol) and boron trifluoride etherate (3 ml). The resulting mixture was stirred at room temperature for 48 hours. The mixture was diluted with dichloromethane (500 ml), washed twice with 10% sodium hydroxide (200 ml), water, and brine, and then dried (Na_2SO_4). The product was concentrated to an oil. A portion was stirred with ether (100 ml) and a crystalline product was formed. The crystalline product was recovered by filtration and purified by recrystallization to yield 4-bromo-1-(1,3-dithian-2-yl)ethylbenzene.

(B) 4-(4-bromobutyl]-1-[1,3-dithian-2-yl) ethylbenzene

A solution of 4-bromo-1-(1,3-dithian-2-yl)ethylbenzene (27.2 g, 94 moles) in tetrahydrofuran (200 ml) was charged with sec-butyllithium (99 ml, 1.3M in cyclohexane, 0.13 mole) dropwise at −78° C. under nitrogen. The mixture was stirred at ambient temperature for 1.5 hours, and then quenched with 1,4-dibromobutane (4.2 g, 0.2 mole). After being stirred for 3 hours, the mixture was poured into ethyl acetate, and then washed with water and brine. The organic solution was then dried (Na_2SO_4) and concentrated to an oil. The crude product was purified by flash chromatography over silica gel column. The 4-(4-bromobutyl)-1-(1,3-dithian-2-yl)ethylbenzene thus purified was a light oil, 22.3 g.

ANALYSIS

Calculated for $C_{15}H_{21}BrS_2$: 52.17% C 6.13% H.

Found: 52.60% C 6.25% H.

(C) 1-[4-(1,3-dithian-2-yl)ethyl]phenyl-4-(6-fluoro-1,2-benzisoxazol-3-yl]butylpiperidine

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5.4 g, 24.5 mmoles), K_2CO_3 (4.2 g, 30 mmoles), 4-(4-bromobutyl)-1-(1,3-dithian-2-yl) ethylbenzene (8.5 g, 24.6 mmoles) in acetonitrile (200 ml) was heated at reflux for 2.5 hours. At the end of the reaction, the mixture was filtered and the solvent was concentrated. The crude (13 g) was purified by flash chromatography over a silica gel column. The material thus purified (8.67 g; 72%) was recrystallized from ethanol (50 ml) and hexane (100 ml) to afford 6.6 g of 1-[4-(1,3-dithian-2-yl)ethyl]phenyl-4-(6-fluoro-1,2-benzisoxazol-3-yl)butylpiperidine as light yellow crystals, m.p.=108°–110° C.

ANALYSIS

Calculated for: 66.91% C 6.86% H 5.78% N.

Found: 66.72% C 6.76% H 5.71% N.

EXAMPLE 104

1-[4-(4'-Acetophenyl)butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine

A solution of 1-[4-(1,3-dithian-2-yl)ethylphenyl]butyl-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (5.6 g, 11.6 mmoles), water (5 ml), and methanol (30 ml), in acetone (50 ml), was treated with mercury (II) perchloroate trihydrate (5 g, 1.1 eq) at room temperature. After 30 minutes, the reaction was completed. The solids were filtered, and the solvent was removed on a rotary evaporator. The crude product was dissolved in ethyl acetate (500 ml) and washed with water, brine, then dried over Na2SO_4. The solvent was removed to give a crude oil. The purification was by flash chromatography over a silica gel column. The oil thus obtained (2.67 g, 50%) was combined with 1.1 g of oil prepared in the same fashion. Crystallization from ethanol (10 ml) and hexane (20 ml) yielded 1-[4-(4'-acetophenyl) butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine as off-white crystals, 2.32 g, m.p.=85°–86° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_2$: 73.07% C 6.90% H 7.10% N.

Found: 72.68% C 7.05% H 7.09% N.

EXAMPLE 105

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3-methoxyphenyl] ethanone

To a stirred suspension of sodium hydride (0.37 g, 0.007 mol of a 50% oil dispersion), in dimethylformamide (20 ml) was added, dropwise, 1-[4-[3-[4-(6-fluoro-1,2-

benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3hydroxyphenyl]ethanone (2.9 g, 0.007 mol) dissolved in dimethylformamide (25 ml). The reaction was stirred at ambient temperature for 15 minutes, and then it was cooled with an ice bath to about 5° C., whereupon methyl iodide (1.0 g, 0.007 mol) in dimethylformamide (1 ml) was added dropwise. The reaction was stirred at ambient temperature for 30 min, and then water was added. The resulting aqueous mixture was extracted with ethyl acetate, the extract washed with water, dried ($MgSO_4$), and the solvent was concentrated to afford 4.9 g of a brown oil, which solidified on standing. The solid was flash chromatographed on silica gel. The appropriate fractions were concentrated to yield 2.7 g of product as a yellow solid. Recrystallization from toluene-hexane yielded 2.0 g (67%) of analytically pure 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propylamino]-3-methoxyphenyl]ethanone as a yellow solid, m.p.=96°–98° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_3$: 67.75% C 6.63% H 9.88% N.

Found: 67.93% C 6.72% H 9.80% N.

EXAMPLE 106

(2,4-Difluorophenyl)-[1-(phenylmethyl)-3-pyrrolidinyl]methanone oxalate

In a 1 l round bottom flask, a solution of ethyl-N-benzyl-3-pyrrolidine carboxylate (21.8 g, 11.7 mmoles) in 140 ml of 6N HCl was heated at reflux for 2.5 hours. The solution was cooled and the solvent was removed to dryness with a vacuum pump. The residue was then treated with thionyl chloride (100 ml) for 16 hours at room temperature. After the reaction, the excess thionyl chloride was vacuum stripped to dryness (60° C., 4 hrs). To the residue in the flask was added 1,3-difluorobenzene (30 g, 26 mmoles) followed by aluminum chloride (25 g, 18.7 mmoles) in portions at room temperature. When the mixture turned homogeneous (in about 10 minutes) it was then heated at 55° C. for 1 hour. After the reaction was complete, excess 1,3-difluorobenzene was removed under reduced pressure. The residue was partitioned between ice/water and dichloromethane (700 ml) and basified with 50% NaOH solution to pH 10. The dichloromethane solution was washed with water and brine, then dried over anhydrous $MgSO_4$. The solvent was stripped and the crude oil (31 g) was purified by flash chromatography over a silica gel column. The pure product thus obtained weighed 26 g (74%) as a yellow oil. An analytical sample was prepared by dissolving 4.2 of the oil in ethanol and treating with an ethanol solution of oxalic acid (1.33 g, 14.8 mmoles). To the mixture was added ether dropwise to cause crystallization. Recrystallization from ethanol and ether gave 2.63 g of (2,4 -difluorophenyl)[1-phenylmethyl)-3-pyrrolidinyl]methanone oxalate as white crystals, m.p.= 114°–116° C.

ANALYSIS

Calculated for $C_{20}H_{19}FNO_5$: 61.38% C 4.89% H 3.58% N.

Found: 61.16% C 4.80% H 3.60% N.

EXAMPLE 107

6-Fluoro-3-[1-phenylmethyl)-3-pyrrolidinyl]-1,2-benzisoxazole fumarate

(A) (2,4-difluorophenyl)[1-(phenylmethyl)-3-pyrrolidinyl]methanone oxime

To the compound (2,4-difluorophenyl)[1-(phenylmethyl)-3-pyrrolidinyl]methanone (22 g) in 95% ethanol (350 ml) and water (100 ml) was added $NH_2OH.HCl$ (10.1 g) and ammonium acetate (12.7 g, 2.1 eq). The resulting mixture was refluxed for 3.5 hours. The mixture was then allowed to stir at room temperature for 24 hours. The reaction mixture was concentrated to remove ethanol, poured into water (500 ml), and extracted with dichloromethane (500 ml). This was followed by washing with water, brine, and drying over magnesium sulfate. The product was concentrated to an oil and purified by column chromatography to yield 12 g of (2,4-difluorophenyl)[1-(phenylmethyl)-3-pyrrolidinyl] methanone oxime.

(B) 6-fluoro-3-[1-(phenylmethyl)-3-pyrrolidinyl]-1, 2-benzisoxazole fumarate

A mixture of (2,4-difluorophenyl)[1-(phenylmethyl)-3-pyrrolidinyl]methanone oxime (10.8 g, 34.2 mmoles), potassium hydroxide (10 g), water (100 ml), and ethanol (100 ml) was heated at reflux for 2 hr. At the end of the reaction, the solution was cooled and ethanol was removed on a rotary evaporator. The aqueous mixture was diluted with water (100 ml) then extracted with dichloromethane (500 ml). The organic solution was washed with brine and dried over anhydrous $MgSO_4$. The solution was concentrated to an oil (9.8 g). The crude product was purified by flash chromatography over a silica gel column. The product thus obtained weighed 4.46 g (44%) as a light yellow oil. The oily product was dissolved in ethanol, and then treated with a solution of fumaric acid (1.73 g, 1.0 eq) in ethanol. Crystallization took place slowly with the addition of isopropyl ether. Recrystallization from ethanol (15 ml) gave 4.6 g of 6-fluoro-3-[1-(phenylmethyl)-3-pyrrolidinyl]-1,2-benzisoxazole fumarate as white crystals, m.p.=142°–144° C.

ANALYSIS

Calculated for $C_{22}H_{21}FN_2O_5$: 64.07% C 5.13% H 6.81% N.

Found: 64.11% C 5.05% H 6.89% N.

EXAMPLE 108

(E)-1-[4-[(4-bromo-2-butenyl)oxy]-3-methoxyphenyl]ethanone

A mixture of 4-hydroxy-3-methoxyacetophenone (10 g, 59 moles), K_2CO_3 (10 g, 1.2 q) and 1,4-dibromo-2-butene (>95% trans, Aldrich, 18 g, 1.2 eq) in acetone (500 ml) was heated at 55° C. for 3 hr. At the end of the reaction, the solvent was concentrated. The crude product was extracted into dichloromethane (750 ml) and the insolubles were filtered; then the solution was concentrated again to an oil. Purification on a silica gel column (SiO_2, 100 g, eluted with dichloromethane) yielded 7.25 g (40%) of white solid. Recrystallization from ether gave analytically pure (E)-1-[4-[(4-bromo-2-butenyl)oxy]-3-methoxyphenyl]ethanone (3.91 g), m.p.=71°–72° C.

ANALYSIS

Calculated for $C_{13}H_{15}BrO_3$: 52.19% C 5.50% H.

Found: 52.12% C 4.94% H.

EXAMPLE 109

4-(3-Chloropropoxy)-3-methoxybenzaldehyde

A mixture of vanillin (30.4 g, 0.2 mol), K_2CO_3 (27.6 g) and acetone (150 ml) was stirred and refluxed for 0.5 hours. Heating was removed and 1-bromo-3-chloropropane (40.8 g, 0.26 mol) in acetone was added dropwise. The reaction was stirred and refluxed for 16 hours, and then it was poured into water. The aqueous mixture was extracted with diethyl

ether, the extract was dried ($MgSO_4$), and the solution, was concentrated to afford an oil, which upon evacuation solidified to a white solid (50.2 g). An 8.0 g sample was flash chromatographed on silica gel with 50% ethyl acetate-hexane as eluent. Concentration of appropriate fractions gave 2.7 g (37%) of 4-(3-chloropropoxy)-3-methoxybenzaldehyde as a white solid m.p.=53°–55° C.

ANALYSIS

Calculated for $C_{11}H_{13}ClO_3$: 57.78% C 5.73% H.

Found: 57.21% C 5.52% H.

EXAMPLE 110

6-Fluoro-3-(3-pyrrolidinyl)-1,2-benzisoxazole hydrochloride

A mixture of 3-(6-fluoro-1,2-benzisoxazol-3-yl)-1-pyrrolidinylcarboxylic acid ethenyl ester (5.1 g, 18.4 mmol, hydrochloride acid (5 ml), and isopropyl alcohol (50 ml) was heated at reflux for 3.5 hr. At the end of the reaction, the solvent was reduced to about 30 ml on a rotary evaporator and the mixture was cooled to 0° C. for 2 hr. The crystals were collected by filtration and rinsed with cold isopropyl alcohol. The 6-fluoro-3-(3-pyrrolidinyl)-1,2-benzisoxazole hydrochloride product weighed 3.09 g (69%), m.p.= 225°–227° C.

ANALYSIS

Calculated for $C_{11}H_{11}FN_2O.HCl$: 54.44% C 4.99% H 11.54% N.

Found: 54.35% C 4.99% H 11.38% N.

EXAMPLE 111

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3-hydroxyphenyl]ethanone

A mixture of N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl-6-acetyl-2-benzoxazolinone (6.0 g, 0.014 mol) and 10% aqueous sodium hydroxide (50 ml) was stirred and refluxed for 40 minutes. Water was added and the reaction was made acidic with 5% hydrochloric acid. Saturated Na_2CO_3 was added until effervescence ceased. The aqueous mixture was extracted with dichloromethane. The dichloromethane extract was washed (water), dried (K_2CO_3) and concentrated to afford 2.6 g of a tacky solid. The crude solid was treated with saturated $NaHCO_3$, and extracted into dichloromethane. The dichloromethane was washed (brine and then water), and dried ($MgSO_4$) yield. The organic extract was then concentrated to 2.4 g of a brown solid, which was combined with another sample to yield 5.0 g. This sample was flash chromatographed on silica. A small sample (0.25 g) was recrystallized from toluene to yield 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propylamino]-3-hydroxyphenyl]ethanone as a brownish solid, 0.15 g, m.p.=150°–152° C.

ANALYSIS

Calculated for $C_{23}H_{26}FN_3O_3$: 67.14% C 6.37% H 10.21% N.

Found: 67.54% C 6.58% H 9.95% N.

EXAMPLE 112

1-[3-Acetylamino-4-[3-chloropropoxy)phenyl] ethanone

A stirred mixture of 1-[3-acetylamino-4-hydroxyphenyl] ethanone (7.7 g, 0.04 mol), K_2CO_3 (5.7 g), 3-chloro-1-bromopropane (8.9 g, 0.056 mol), and acetone (100 ml) was refluxed for 16 hours. The reaction was allowed to cool to ambient temperature, and filtered. Concentration of the filtrate yielded 8.5 g of a white solid. The solid was recrystallized from toluene and then from ethanol to afford 6.5 g of an off-white solid. A 3.3 g sample of this material was flash chromatographed on silica gel. Concentration of the appropriate fractions afforded 2.8 g of a white solid. The solid was recrystallized from toluene and then from ethanol-water to yield 2.2 g (51%) of 1-[3-acetylamino-4-(3-chloropropoxy)phenyl]ethanone as a white solid, m.p.= 124°–126° C.

ANALYSIS

Calculated for $C_{13}H_{16}ClNO_3$: 57.89% C 5.98% H 5.19% N.

Found: 57.08% C 5.85% H 5.13% N.

EXAMPLE 113

N-[2-(3-hydroxypropoxy)phenyl]acetamide

A stirred mixture of 2-hydroxyphenylacetamide (10.0 g, 0.066 mol), K_2CO_3 (6.9 g), 3-bromopropanol (12.8 g, 0.012 mol), and acetone (250 ml) was refluxed for 16 hours. The reaction mixture was allowed to cool, and then it was filtered. The filtrate was concentrated to yield 19.0 g of a thick, broom oil. The oil was distilled with a Kugelrohr apparatus and 11.2 g (82%) of a viscous, orange oil was collected. The oil solidified upon standing. An analytical sample was obtained by recrystallization from ethyl acetate to afford the alcohol as an off-white solid m.p.=78°–80° C.

ANALYSIS

Calculated for $C_{11}H_{15}NO_3$: 63.14% C 7.23% H 6.69% N.

Found: 63.10% C 7.32% H 6.64% N.

EXAMPLE 114

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] butyl bromide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (12 in, 55 mmol), K_2CO_3 (13 m) and 1,4-dibromobutane (20 m, 9.3 mmol, 1.7 eq) in acetonitrile (300 ml) was stirred at room temperature overnight. The inorganic material was filtered. The solution was concentrated to ~80 ml, when crystals crashed out. The product was filtered to yield 14.16 m (73%), m.p.=243°–245° C.

ANALYSIS

Calculated for $C_{16}H_{20}BrFN_2O$: 54.09% C 5.67% H 7.89% N.

Found: 54.13% C 5.52% H 7.83% N.

EXAMPLE 115

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl acetate fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 gm, 13.6 mmol), K_2CO_3 (3.5 m, 25 mmol), 2-bromoethyl acetate (4 gm, 26.5 mmol) in acetonitrile (50 ml) was heated at reflux for 4 hr. After cooling to room temperature, the inorganic salts were filtered and washed with DCM (dichloromethane 50 ml). The organic solvent was removed on a rotary evaporator to give an oil. The oily product was purified on a flash chromatography column (60 gm of SiO_2; eluted with MeOH 2%–4% in DCM). The pure product thus obtained weighed 4.43 gm. This oil was dissolved in ethanol and treated with a solution of fumaric acid (1.2 gm) in ethanol. The salt crystallized out at room temperature to yield 3.44 gm (57%), m.p.= 154°–155° C.

ANALYSIS

Calculated for $C_{16}H_{19}FN_2O_3.C_4H_4O_4$: 56.86% C 5.49% H 5.63% N.

Found: 56.75% C 5.41% H 6.54% N.

EXAMPLE 116

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]morpholine

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 gm, 13.6 mmol), 2-chloroethyl morpholine hydrochloride (4.46 gm, 29.7 mmol) and K_2CO_3 (7.3 gm, 2.2 eq) in acetonitrile (60 ml) was heated at reflux for 24 hr. The crude mixture was diluted with DCM and filtered. The solvent was concentrated to an oil (~7.1 gm). Purification on a silica gel column (55 gm, SiO_2, eluted with MeOH:DCM) yielded a solid product weighing 4 gm. Recrystallization from hot ethanol yielded 2.1 gm (48%), m.p.=131°–132° C.

ANALYSIS

Calculated for $C_{18}H_{24}FN_3O_2$: 64.84% C 7.26% H 12.60% N.

Found: 64.80% C 7.09% H 12.77% N.

EXAMPLE 117

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]phthalimide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5 15 gm 23 4 mmol) K_2CO_3 (4.2 gm, 30.4 mmol) and 2-bromoethyl phthalimide (7.13 gm, 28 mmol) in acetonitrile (250 ml) was heated at reflux for 3.5 hr. The solids and solvent were removed. The residue was purified by flash chromatography (SiO_2, 110 m, eluted with 2–4% CH_3OH:DCM). The product thus obtained weighed 7.8 gm (84%). Part of the material was recrystallized to give 2.35 gm of off white crystals, m.p.=148°–149° C.

ANALYSIS

Calculated for $C_{22}H_{20}FN_3O_3$: 67.17% C 5.12% H 10.68% N.

Found: 67.01% C 5.20% H 10.76% N.

EXAMPLE 118

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl methyl ether fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.75 gm, 17 mmol), K_2CO_3 (3 gm, 21.7 mmol), bromoethyl methyl ether (2.84 gm, 20.4 mmol) in acetonitrile (150 ml) was heated at reflux for 3.5 hr. The reaction was cooled. The inorganics were filtered and rinsed with DCM. The organic solution was concentrated down to an oil (7 gm). Purification on a flash chromatography column (SiO_2, 45 gm; eluted with methanol/DCM) gave a light yellow oil as product (4 gm, 87%). This oil was dissolved into ethanol and treated with a solution of fumaric acid (1.67 gm) in ethanol (20 ml). White crystals (5.15 gm) were collected, m.p.=157°–158° C.

ANALYSIS

Calculated for $C_{15}H_{19}FN_2O_2.C_4H_4O_4$: 57.86% C 5.88% H 7.10% N.

Found: 57.53% C 5.94% H 6.94% N.

EXAMPLE 119

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] butyl acetate fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (9.5 gm; 41 mmol), K_2CO_3 (7.2 m, 51 mmol), and 4-bromobutyl acetate (10 gm, 51 mmol) in acetonitrile (200 ml) was heated at reflux for 3½ hr. At the end of the reaction, the solution was cooled and filtered. The inorganic salt was washed with DCM (50 ml). The organic solvent was removed. The residue was purified on a flash chromatography column (packed with Sorbsil C30 silica gel, 100 gm, eluted with DCM, 1 liter, increasing methanol from 2 to 4%, 2.51). The material thus purified weighed 12.92 gm (89%). A small sample (1.67 gm) was dissolved in ethanol and treated with 1 equivalent of fumaric acid (580 mg) in ethanol to yield white crystals: 1.8 gm, m.p.=142°–143° C.

ANALYSIS

Calculated for $C_{18}H_{23}FN_2O_3.C_4H_4O_4$: 58.66% C 6.04% H 6.22% N.

Found: 58.56% C 6.02% H 6.13% N.

EXAMPLE 120

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] butanol fumarate

A mixture of 4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl acetate (11.5 gm, 34.4 mmol), 15% NaOH (100 ml) and ethanol (100 ml) was heated at reflux for 4 hrs. After cooling to room temperature, the base was neutralized with HCl to pH=7. The solution was concentrated down to a small volume ml), then extracted with DCM. The DCM solution was washed with brine and dried over $MgSO_4$. The solvent was concentrated to give ~^{10} gm of crude oil. Purification by flash chromatography (Sorbsil C-30, 100 gm, eluted with MeOH:DCM, 3 liters) yielded 9.8 gm of white solid. The sample for testing was prepared by treatment of the free base (2.0 gm) with fumaric acid (780 mg, 1.0 eq) in ethanol. The crystals were collected and dried: 1.5 gm, m.p.=131°–132° C.

ANALYSIS

Calculated for $C_{16}H_{21}FN_2O_2.C_4H_4O_4$: 58.82% C 6.17% H 6.86% N.

Found: 58.81% C 6.37% H 6.66% N.

EXAMPLE 121

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] butyl decanoate fumarate

To a solution of 4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butanol (2.0 gm, 6.84 mmol), triethylamine (1.0 gm, 10 mmol) in DCM (70 ml) decanoyl chloride (1.7 gm, 8.9 mmol) was added dropwise at room temperature. The mixture was stirred for 1 hr., then was concentrated to a crude solid. The solid was extracted into ethyl acetate, and the insoluble salts were filtered. The solvents were removed. The crude product was purified by flash chromatography (Sorbsil C-30, 30 in, eluted -with a mixture of MeOH in DCM). The oil thus obtained (2.5 gm, 81%) was converted to a fumarate salt with fumaric acid (650 mg), 1.0 eq) in ethanol. Crystals were collected: 1.48 gm, m.p.=109°–110° C.

ANALYSIS

Calculated for $C_{26}H_{39}FN_2O_3.C_4H_4O_4$: 64.04% C 7.70% H 4.98% N.

Found: 64.30% C 7.86% H 4.78% N.

EXAMPLE 122

3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propyl decanoate fumarate

To a solution 3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propanol (1.81 gm, 6.5 mmol) triethylamine (0.9

gm, 9.0 mmol) in DCM (45 ml) was added decanoyl chloride (1.5 gm, 7.8 mmol) dropwise at room temperature. The mixture was stirred for 20 minutes, then concentrated down to a crude solid. The solid was extracted into EtOAc (20 ml), and the insoluble salts were filtered. The EtOAc was removed. The crude oil was purified by flash chromatography (Sorbsil C-30, 30 gm; eluted with MeOH:DCM). The oil thus obtained (2.54 gm, 90%) was converted to a fumarate salt with fumaric acid (670 mg) in ethanol. The crystals collected weighed 1.61 gm, m.p.=100°–102° C.

ANALYSIS

Calculated for $C_{25}H_{27}FN_2O_3.C_4H_4O_4$: 63.52% C 7.54% H 5.11% N.

Found: 63.63% C 7.74% H 5.03% N.

EXAMPLE 123

N,N-Diethyl-4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl carbamate fumarate

To a mixture of 4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butanol (1.55 gm, 5.3 mmol) potassium t-butoxide (750 mg, 6.7 mmol) in THF (100 ml), diethylcarbamyl chloride (900 mg, 6.63 mmol) was added dropwise at room temperature. The mixture was stirred for 2 hr, then the solvent was removed. The residue was extracted into DCM. The DCM solution was washed with brine and dried over $MgSO_4$. The solution was concentrated. The product was purified on a flash chromatography column (SiO_2, 14 gm, eluted with 2% MeOH in DCM), to yield 1.84 gm of oil. This oil was dissolved into ethanol (~5 ml) and treated with a solution of fumaric acid (850 mg, 1.0 eq) in ethanol. Crystallization was induced with a small volume of isopropyl ether to produce 2.09 gm, m.p.=152°–153° C.

ANALYSIS

Calculated for $C_{21}H_{30}FN_3O_3.C_4H_4O_4$: 59.16% C 6.75% H 8.28% N.

Found: 59.17% C 6.84% H 8.16% N.

EXAMPLE 124

N-Methyl-4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl carbamate fumarate

To a mixture of 4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butanol (1.84 gm, 6.3 mmol), K_2CO_3 (850 mg) in chloroform, methyl isocyanate (448 mg, 7.7 mmol and 360 mg, 6.2 mmol) was added dropwise in two portions. The mixture was filtered and concentrated to a crude oil. Purification was done on a flash chromatography column (SiO_2, 11 gm, eluted with 2% CH_3OH in DCM) to yield a light yellow oil (2.05 gm, 93%). This oil was dissolved into ethanol and treated with a solution of fumaric acid (800 mg, 1.0 eq). Crystallization was induced with drops of isopropyl ether. Weight: 1.36 in, m.p.=96°–98° C.

ANALYSIS

Calculated for $C_{18}H_{24}FN_3O_3.C_4H_4O_4$: 56.76% C 6.06% H 9.02% N.

Found: 56.27% C 6.03% H 8.86% N.

EXAMPLE 125

2-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,3-dioxane fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.0 gm, 9.1 mmol), K_2CO_3 (1.5 gm, 10.9 mmol) and bromoethyl-1,3-dioxane (2.1 gm, 10.7 mmol) in acetonitrile (50 ml) was heated at reflux for 3 hr. At the end, the insolubles were filtered and rinsed with DCM and the filtrate was evaporated down. The crude mixture was purified by flash chromatography over a silica gel column (Sorbsil C-30, 25 gm; eluted with DCM and MeOH (1–3%) in DCM). The fractions containing the pure product were combined and concentrated to give 3.13 gm of oil. The oil was treated with a fumaric acid (1.0 in) ethanol solution. The crystals were collected: 3.98 gm (77%), m.p.=161°–162° C.

ANALYSIS

Calculated for $C_{18}H_{23}FN_2O_3.C_4H_4O_4$: 58.66% C 6.04% H 6.22% N.

Found: 58.69% C 5.96% H 6.20% N.

EXAMPLE 126

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl-1-piperidinyl] ethanol hemifumarate

(A) 2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl acetate

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl acetate was prepared according to Example 115.

(B) 2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl-1-piperidinyl]ethanol hemifumarate

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl acetate (10.58 gm, 34.6 mmol), 15% NaOH (100 ml) and ethanol (100 ml) was heated at reflux for 4 hr. The solution was cooled (~5° C.) and neutralized with HCl to pH~7. The ethanol was removed under reduced pressure. The aqueous solution was basified with $NaHCO_3$ and extracted with DCM (2x200 ml). The DCM solution was washed with brine and dried over $MgSO_4$ and evaporated to give a white solid: 6.88 gm (75%). A sample (2.03 gm) was dissolved in ethanol and treated with fumaric acid (600 mg, 1.0 eq). Crystallization was induced with drops of isopropyl ether to yield off-white crystals: 143 in, m.p.=159°–161° C.

ANALYSIS

Calculated for $C_{14}H_{17}FN_2O_2.0.5C_4H_4O_4$: 59.62% C 5.94% H 8.69% N.

Found: 59.55% C 5.95% H 8.53% N.

EXAMPLE 127

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl decanoate fumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl alcohol (1.6 gm, 5 mmol) and triethylamine (800 mg, 8 mmoles) in chloroform (100 ml) was treated with decanoyl chloride (1.3 gm, 7.2 mmol) dropwise at room temperature. The mixture was stirred for 4 hours. The solvent was removed to leave a crude solid. The solid was dissolved into a small amount of DCM (15 ml), then was filtered. The solution was concentrated.

The purification was done by flash chromatography over a silica gel column (Sorbsil C-30, 30 gm; eluted with MeOH: DCM). The purified oil (2.45 gm, 95%) was treated with a fumaric acid (660 gm, 1.0 eq)/ethanol solution (15 ml). Crystallization was induced by adding drops of ether; yield: 1.97 gm, m.p.=109°–110° C.

ANALYSIS

Calculated for $C_{24}H_{35}FN_3O_3.C_4H_4O_4$: 62.90% C 7.35% H 5.24% N.

Found: 62.93% C 7.30% H 5.14% N.

EXAMPLE 128

N,N-Diethyl-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylcarbamate fumarate

To a mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethanol (1.6 gm, 6 mmol) and potassium

t-butoxide (860 mg, 7.6 mmol) in THF (100 ml) diethyl carbamyl chloride (1.03 gm, 7.5 mmol) was added dropwise at room temperature. The mixture was stirred for 4 hr. The reaction mixture was concentrated to a crude solid. The solid was dissolved in DCM and purified on a flash chromatography column (Sorbsil C-30, 27 gm; eluted with a MeOH: DCM mixture). The product thus purified as a light oil (2.2 gm, 91%) was dissolved into ethanol and treated with a fumaric acid (690 mg, 1.0 eq)/ethanol solution (15 ml). Crystallization on cooling yielded 2.15 gm of white crystals, m.p.=133°–135° C.

ANALYSIS

Calculated for $C_{19}H_{26}FN_3O_3.C_4H_4O_4$: 57.61% C 6.31% H 8.76% N.

Found: 57.49% C 6.25% H 8.54% N.

EXAMPLE 129

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethylamine hemifumarate

(A) 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl phthalimide

2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl phthalimide was prepared according to Example 117.

(B) 2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine hemifumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl phthalimide (4.6 in, 11.7 mmol) and hydrazine monohydrate (1.17 gm, 23.4 mmol) in methanol (50 ml) was heated at reflux overnight. At the end of the reaction, methanol was removed to leave a crude solid. This was stirred with water (150 ml) and acidified with HCl to pH=2. The insolubles were filtered. The aqueous solution was basified with 50% NaOH then extracted with DCM (2x250 ml). The DCM solution was washed with brine and dried over $MgSO_4$. The solvent was removed to produce a colorless oil: 2.12 gm. This oil was treated with a solution of fumaric acid (935 mg, 1.0 eq) in ethanol. The salt crystallized out: 0.99 gm, 203°–205° C. A second crop of 0.73 in (m.p.=198°–200° C.) was collected later.

ANALYSIS

Calculated for $C_{14}H_{18}FN_3O.0.5C_4H_4O_4$: 59.80% C 6.27% H 13.07% N.

Found: 59.51% C 6.35% H 13.31% N.

EXAMPLE 130

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl decanamide fumarate

To a mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (1.49 gm, 5.5 mmol) and triethylamine (1.0 gm, 10 mmol) in chloroform (50 ml) decanoyl chloride (1.26 gm, 6.6 mmol) was added at room temperature. The mixture was stirred for 3 hr at room temperature. The solvent was stripped down to a crude mixture. This crude mixture was purified by flash chromatography over a silica gel column (SiO_2, 20 gm; eluded with a solution of MeOH (0–3%) in DCM). The fractions containing the pure product were pooled and concentrated to give 2.3 gm of oil. This oil was converted to a fumarate salt by treatment with fumaric acid (655 mg) in ethanol. The ethanol was concentrated down to a small volume and 3 volumes of isopropyl ether was added. This mixture was stirred overnight to cause crystallization. The solids were collected, weighed: 1.83 gm (60.5%), m.p.=108°–110° C.

ANALYSIS

Calculated for $C_{24}H_{36}FN_3O_2.C_4H_4O_4$: 63.02% C 7.56% H 7.87% N.

Found: 62.42% C 7.58% H 7.66% N.

EXAMPLE 131

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl acetamide fumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.56 g, 9.7 mmol) and triethylamine (1.45 gm, 14.5 mmol) in DCM (50 ml) was treated with dropwise addition of acetyl chloride (1.0 gm, 12.7 mmol) at room temperature. The mixture was stirred for 4 hr at room temperature. The reaction mixture was diluted with DCM and washed with brine. The organic solution was dried over $MgSO_4$ and concentrated to a crude oil. The crude oil was purified by flash chromatography over a silica gel column (SiO_2, 20 gm; eluted with (0–2%) CH_3OH in DCM). The pure product thus obtained weighed 1.36 gm (46%). It was converted to a fumarate salt by treatment with fumaric acid (517 mg) in ethanol. Recrystallization from ethanol gave white crystals; weight: 1.53 gm, m.p.=132°–133° C.

ANALYSIS

Calculated for $C_{16}H_{20}FN_3O_2.C_4H_4O_4$: 57.00% C 5.74% H 9.97% N.

Found: 57.05% C 5.85% H 9.95% N.

EXAMPLE 132

2-[[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]amino]ethyl acetate fumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.0 gm, 7.6 mmol), K_2CO_3 (1.38 gm, 10 mmol) and bromoethyl acetate (1.40 gm, 8.3 mmol) in acetonitrile (50 ml) was heated at reflux for 4 hr. At the end, the insolubles were filtered off and rinsed with DCM. The solvent was evaporated down. The crude mixture was purified by flash chromatography over a silica gel column (Sorbsil C-30, 30 gm; eluted with 2% CH_3OH in DCM, 800 ml). The oil (1.15 gm) thus obtained was treated with a solution of fumaric acid (358 mg) in ethanol. Crystallization was induced by adding drops of ethyl ether, yield: 1.09 gm, m.p.=116°–118° C.

ANALYSIS

Calculated for $C_{18}H_{24}FN_3O_3.C_4H_4O_4$: 56.77% C 6.06% H 9.03% N.

Found: 56.32% C 5.97% H 8.94% N.

EXAMPLE 133

N-[2-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]carbamate fumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.0 gm, 7.6 mmol) and triethylamine (1.0 gm, 10 mmol) in DCM (50 ml) was treated with methyl chloroformate (860 mg, 9.12 mmol) dropwise at room temperature. The mixture was stirred for 1 hr. The reaction mixture was diluted with DCM and washed with brine. The organic solution was dried over $MgSO_4$ and concentrated to a crude oil. The purification was done by flash chromatography over a silica gel column (28 gm of Sorbsil C-30, eluted with DCM and MeOH/DCM). The pure oil thus obtained weighed 2.34 gm. It was converted to a fumarate salt by treatment with fumaric acid (840 mg, 1.0 eq) in ethanol. Crystallization was induced by adding drops of isopropyl ether, yield: 2.31 gm, m.p.=163°–165° C.

ANALYSIS

Calculated for $C_{16}H_{20}FN_3O_3.C_4H_4O_4$: 54.92% C 5.53% H 9.61% N.

Found: 54.49% C 5.45% H 9.24% N.

EXAMPLE 134

Z-2-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]hexahydro-1H-isoindole-1,3-dione fumarate

A mixture of 1-(2-aminoethyl)-4-(6-fluoro-1,2-benzisoxazol-3yl)piperidine (3.77 gm, 14.3 mmol) and cis-1,2-cyclohexanedicarboxylic anhydride (2.82 gm, 18.2 mmol, 1.25 eq) in dry pyridine (50 ml) was heated at 65° C. for 48 hr. The dark brown solution was concentrated to dryness on a rotary evaporator. The crude residue was purified twice by flash chromatography over a silica gel column (SiO_2, 45 gm and 50 gm, eluted with DCM and 1% CH_3OH in DCM). The pure product thus obtained 2.35 gm (41%), was converted to the fumarate salt by treatment with fumaric acid (660 mg) in ethanol. The crystals after two recrystallizations weighed 1.37 gm, m.p.=172°–173° C.

ANALYSIS

Calculated for $C_{22}H_{26}FN_3O_3.C_4H_4O_4$: 60.57% C 5.87% H 8.15% N.

Found: 60.40% C 5.55% H 7.82% N.

EXAMPLE 135

(S)-(+)-13-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol fumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidine (7.2 gm, 32.7 mmol), (S)-(+)-3-bromo-2-methyl-1-propanol (5.0 gm, 32.6 mmol), K_2CO_3(7.19 gm, 52 mmol) in acetonitrile (250 ml) was heated at reflux overnight. The insolubles were filtered off. The solvent was removed at reduced pressure and the crude residue was purified by silica gel chromatography (SiO_2, 84 gm, eluted with 21 of 1% CH_3OH in DCM) to give the target compound as an off-white solid (8.83 in, 94%). A sample of 1.7 gm was converted to the fumarate salt by treatment with fumaric acid (710 mg) in ethanol. Recrystallization from ethanol yielded 1.74 gm of white crystals, m.p.=119°–12.1° C.

ANALYSIS

Calculated for $C_{20}H_{25}FN_2O_6$: 58.82% C 6.17% H 6.86% N.

Found: 58.81% C 6.24% H 6.76% N.

EXAMPLE 136

4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-[3-(1-piperidinyl]propyl]piperidine difumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidine (3.0 gm, 13.6 mmol), N-(3-chloropropyl) piperidine hydrochloride (4.05 gm, 20.4 mmol), K_2CO_3 (6 gm, 43.4 mmol), tetrabutyl-ammonium hydrogen sulfate (phase transfer catalyst, 2.3 gm) in acetonitrile (100 ml) and water (15 ml) was heated at reflux for 16 hr. The mixture was washed with brine and the layers were separated. The organic solution was concentrated. The crude product (6.4 gm) was purified by flash chromatography over a silica gel column (55 gm, sorbsil C-30; eluted with 2% CH_3OH:0°–5% DEA in DCM, 1.41). The oil thus purified (4.5 gm) was treated with fumaric acid (1.6 gm) in ethanol. The solid was collected: weight 3.1 in, m.p.178°–181° C. Recrystallization from ethanol yielded 2.28 gm of white crystals, m.p.=190°–192° C.

ANALYSIS

Calculated for $C_{20}H_{24}FN_3O.2C_4H_4O_4$ 58.22% C 6.28% H 7.27% N.

Found: 58.39% C 6.36% H 7.34% N.

EXAMPLE 137

1-(3-Dimethylaminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine difumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.05 gm, 13.8 mmol), 3-dimethylaminopropyl chloride hydrochloride (3.4 gm, 21 mmol), K_2CO_3 (6.2 gm 45 mmol), tetrabutylammonium hydrogen sulfate (phase transfer catalyst, 1.5 gm) in acetonitrile (100 ml) and water (50 ml) was heated at 60° C. overnight. The aqueous phase was separated, the acetonitrile was removed at reduced pressure. The residue was extracted into DCM. The organic solution was washed with H_2O and brine, then dried with $MgSO_4$. The solvent was removed and the crude product (4.3 gm) was treated with fumaric acid (1.58 gm, 1.0eq) in dilute ethanol. The crystals were collected (2.53 gm), m.p.=192°–194° C. Recrystallization from ethanol yielded 2.08 gm of white crystals, m.p.=194°–195° C.

ANALYSIS

Calculated for $C_{17}H_{24}FN_3O_2.C_4H_4O_4$: 55.86% C 6.00% H 7.82% N.

Found: 56.11% C 5.94% H 7.86% N.

EXAMPLE 138

(R)-(–)-3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol fumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidine (14.5 gm, 65 mmol), K_2CO_3 (10 gm, 72 mmol), (R)-(–)-3-bromo-2-methyl-1-propanol (10 gm, 65.3 mmol), tetrabutylammonium hydrogen sulfate (1.27 gm, phase transfer catalyst) in acetonitrile (300 ml) and H_2O (5 ml) was heated at reflux for 6 hr. The mixture was cooled and the solvent was removed on rotary evaporator. The residue was extracted into methylene chloride (DCM), and the insolubles were filtered. After concentration of the extract, the crude product was purified by flash chromatography over a silica gel column (SiO_2, 1.50 gm; eluted with DCM, 11; 2% CH_3OH in DCM, 1.61). The material thus purified weighed 17 gm (89%). The sample for testing was prepared by treatment of a sample (2.28 gm) with fumaric acid (953 mg) in ethanol. The crystals formed slowly upon addition of isopropyl ether. These were collected and dried: weight 1.84 gm, m.p.=114°–115° C.

Elemental ANALYSIS

Calculated for $C_{16}H_{21}FN_2O_2.C_4H_4O_4$: 58.82% C 6.17% H 6.85% N.

Found: 58.48% C 6.08% H 6.57% N.

EXAMPLE 139

3-[1-[3-[4-(1-Methoxyethyl)-2-hydroxyphenoxyl] propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5.7 gm, 26.0 mmol), 4-(3-chloropropoxy)-3-hydroxy-α-methylbenzenemethanol (6.0 g, 26.0 mmol), $NaHCO_3$ (2.4 g, 28.6 mmol), KI (200 mg) and CH_3CN (150 ml) was stirred at reflux under N_2 for 17 hours. A TLC allowed a trace of the alkylating side chain, therefore additional 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (0.6

g, 2.7 mmol) and $NaHCO_3$ (0.22 g, 2.6 mmol) was added and the reaction was refluxed 3 hours longer. The cooled reaction was concentrated and the residue was partitioned between EtOAc and H_2O. The EtOAc extract was washed with H_2O then brine and after drying with $MgSO_4$ the extract was concentrated to yield 11.9 g of a beige oil. The sample was purified by preparative HPLC (Water's Associates Prep LC/System 500 utilizing 2 silica gel columns and eluting with 5% MeOH—CH_2Cl_2). Concentration of later fractions afforded 4.2 g of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylbenzenemethanol. Concentration of earlier fractions gave 4.0 g of a mixture of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylbenzenemethanol and 3-[1-[3-[4-(1-methoxyethyl)-2-hydroxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole (the latter was apparently formed by the reaction of the former with MeOH on silica gel).

The mixture was dissolved in anhydrous Et_2O (330 ml) and anhydrous MeOH (100 ml) and ethereal HCl was added. After stirring 1.5 hours, anhydrous Et_2O was added and the resultant solid was collected and dried to yield 2.9 g of a mixture of the respective HCl salts. The solid was suspended in H_2O and was basified with NH_4OH. The aqueous mixture was extracted with CH_2Cl_2 and the extract was washed with H_{20}, dried with $MgSO_4$ and concentrated to yield 2.7 g of a light beige oil. The oil was purified by preparative HPLC (Water's Associates Prep LC/System 500 using 2 silica gel columns and 3% MeOH—CH_2Cl_2 as eluent). Concentration of later fractions yielded 0.5 g of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylbenzenemethanol. Concentration of earlier fractions gave an oil that solidified upon standing. The product was triturated with heptane and filtered to yield 1.2 g of a white powder. The compound was recrystallized from EtOH to provide 1.1 g (10%) of 3-[1-[3-[4-(1-methoxyethyl)-2-hydroxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole as clean white crystals m.p.=98°–100° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_2O_4$: 67.27% C 6.82% H 6.54% N. Found: 67.18% C 6.84% H 6.54% N.

EXAMPLE 140

6-Fluoro-3-[1-[3-[(1H-indol-5-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.6 g, 11.8 mmol), K_2CO_3 (1.6 g, 11.6 mmol), KI (200 mg), 5-(3-chloropropoxy)indole (2.2 g, 10.5 mmol) and CH_3CN (100 ml) was stirred at reflux under N_2 for 18 hours. The cooled reaction was poured into H_2O and the aqueous mixture was extracted with EtOAc. The EtOAc extract was washed 2 times with H_2O, 2 times with brine and after drying with $MgSO_4$ the solvent was removed in vacuo to yield 5.1 g of a dark oil. The oil was purified by preparative HPLC (Water's Associates Prep LC/System 500, using 2 silica gel columns and 4% MeOH—CH_2Cl_2 as eluent) to afford 2.65 g (65%) of a beige solid. Recrystallization from ethanol gave 2.2 g (54%) of a beige powder, m.p.=118°–121° C.

ANALYSIS

Calculated for $C_{23}H_{24}FN_3O_2$: 70.21% C 6.15% H 10.68% N.

Found: 69.80% C 6.21% H 10.78% N.

EXAMPLE 141

6-Fluoro-3-[1-[3-[(isoquinol-5-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole sesquifumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.8 g, 0.013 mol), 5-(3-chloropropoxy) isoquinoline (2.8 g, 0.013 mol), K_2CO_3 (1.7 g) and CH_3CN (50 ml) was refluxed for 16 h. The reaction was filtered and the filtrate was concentrated to an oil. The filter cake was treated with H_2O, and the aqueous suspension was extracted with CH_2Cl_2. The filtrate was also extracted with CH_2Cl_2, and the extracts were combined, washed (H_2O), dried (K_2CO_3) and concentrated to yield 5.4 g of a brown oil. The oil was purified by HPLC on silica gel columns, eluting with CH_2Cl_2/MeOH (5%), to afford 2.3 g of a yellow oil. The oil was dissolved in EtOAc and fumaric acid (0–66 g, 1 eq) was added. The mixture was refluxed briefly, and then stirred at ambient temperature for 16 h. The resulting white solid was collected to afford 2.2 g of the fumarate salt. The compound was recrystallized from DMF to yield 1.4 g (18.6%) of the isoquinoline as a sesquifumarate, m.p.=213°–215° C.

ANALYSIS

Calculated for $C_{30}H_{30}FN_3O_8$: 62.17% C 5.22% H 7.25% N.

Found: 62.01% C 5.11% H 7.28% N.

EXAMPLE 142

6-Fluoro-3-[1-[3-[(1-H-indol-4-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.5 g, 16 mmol), K_2CO_3 (2.2 g, 16 mmol), KI (200 mg), 4-(3-chloropropoxy)indole (3.0 g, 14 mmol) and CH_3CN (100 ml) was stirred at reflux under N_2 for 7 hours and then at ambient temperature for 68 hours. Reflux was resumed for an additional 6 hours whereupon a TLC revealed incomplete reaction. K_2CO_3 (0.5 g, 4 mmol) was added and the reaction was stirred at reflux for 17 hours. The cooled reaction was poured into H_2O and the aqueous mixture was extracted with EtOAc. The organic extract was washed with H_2O and saturated NaCl and after drying over $MgSO_4$ the solvent was removed to afford 5.7 g of a beige solid. The product was purified by preparative HPLC (Water's Associates Prep LC/System 500 using 2 silica gel columns and 4% MeOH—CH_2Cl_2 as eluent) to yield 3.4 g (61%) of a beige solid. Two consecutive recrystallizations from EtOH provided 2.3 g (41%) of a white powder, m.p.=129°–131° C.

ANALYSIS

Calculated for $C_{23}H_{24}FN_3O_2$: 70.21% C 6.15% H 10.68% N.

Found: 69.90% C 6.15% H 10.65% N.

EXAMPLE 143

6-Fluoro-3-[1-[3-[(6-methoxy-1H-indol-5-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole hemifumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 14 mmol), 5-(3-chloropropoxy)-6-methoxyindole (3.0 g, 13 mmol), K_2CO_3 (2.1 g, 14 mmol), KI (200 mg) and CH_3CN (150 ml) was stirred at reflux under N_2 for 48 hours. The cooled reaction was poured into H_2O and the aqueous mixture was extracted with EtOAc. The EtOAc extract was washed with H_2O and brine and was dried with $MgSO_4$. Removal of the solvent in vacuo gave 5.6 g of a dark oil. The oil was purified by preparative HPLC (Water's Associates Prep LC/System 500 using 2 silica gel columns and 2% Et_2NH-EtOAc as eluent) to yield 2.5 g (47%) of a beige solid. Recrystallization from EtOH afforded 2.0 g of an off White powder. A 1.8 g (4 mmol) sample was dissolved in warm EtOAc and fumaric acid (0.5 g, 4 mmol) was added. The reaction was stirred at ca 40° C.

for 30 minutes and was then allowed to gradually cool to ambient temperature. The resultant hemifumarate salt was collected and dried to yield 2.0 g. The product was recrystallized from EtOH to provide 1.5 g (25%) of a light being powder m.p.=186°–188° C.

ANALYSIS

Calculated for $C_{26}H_{28}FN_3O_5$: 64.84% C 5.87% H 8.73% N

Found: 64.22% C 5.85% H 8.55% N.

EXAMPLE 144

1-[4-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (2.4 g, 10.1 mmol), 1-[4-(3-chloropropoxy)-3-hydroxyphenyl]ethanone (2.5 g, 11.1 mmol), $NaHCO_3$ (0.94 g, 11.1 mmol), KI (100 mg) and CH_3CN (100 ml) was stirred at reflux under N_2 for 65 hours. The cooled reaction was poured into H_2O and the aqueous mixture was extracted with EtoAc. The EtoAc extract was washed with H_2O (1×) and brine (3×) and after drying with $MgSO_4$ the solvent was evaporated to give 4.2 g of a dark solid. Three consecutive recrystallizations from EtOH provided 2.1 g (48%) of glittery beige crystals m.p.=135°–137° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_3S$: 64.47% C 5.88% H 6.54% N.

Found: 64.44% C 5.69% H 6.29% N.

EXAMPLE 145

4-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-alpha-methylbenzenemethanol

To a stirred solution of 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]3-methoxyphenyl]ethanone (4.1 g, 9.3 mmol), in 60 ml MeOH-THF (1:1) under N_2 at ambient temperature, $NaBH_4$ (0.386 g, 10.2 mmol) was added portionwise. After complete addition, the reaction was stirred for 3.5 hours and was concentrated to yield a white gum. This was triturated with H_2O (2×) and the aqueous fraction was decanted away. Residual water was removed under high vacuum to afford 5.0 g of a white powder. The compound was taken up in boiling toluene and the insolubles were filtered away. Concentration of the toluene filtrate afforded 3.8 g of a beige solid. Purification via preparative HPLC (Water's Associates prep LC/System 500, using 2 silica gel columns and 2% Et_2NH-EtoAc) provided 2.7 g of a light beige solid. The product was recrystallized from EtoAc to afford 1.7 g (42%) of a pure white powder, m.p.=113°–115° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_2O_3S$: 64.84% C 6.58% H 6.30% N.

Found: 64.85% C 6.44% H 6.19% N.

EXAMPLE 146

(R)-(–)-3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propyl acetate fumarate

To a mixture of (R)-(–)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol (3.2 gm, 11 mmoles), triethylamine (3.2 gm, 11 mmoles) in DCM (100 ml), acetyl chloride (890 mg, 11.3 mmoles) was added dropwise at 0° C. The mixture was stirred at room temperature for 4½ hrs. The solvent was removed on a rotary evaporator. The triethylamine HCl salt was filtered off using a small amount of DCM. The crude product was dissolved in DCM was purified by flash chromatography over a silica gel column (SiO_2, 30 gm; eluted with DCM and 1% CH_3OH in DCM). The oil, thus purified, weighed 2.11 gm (58%). This oil was treated with a solution of fumaric acid (695mg, 1.0 eq.) in ethanol give the fumarate salt. Recrystallization from ethanol and isopropyl ether again yielded white crystals, 2.09 gm, m.p.=118°–120° C.

ANALYSIS

Calculated for $C_{18}H_{23}FN_2O_3.C_4H_4O_4$: 58.66% C 6.04% H 6.22% N.

Found: 58.53% C 5.76% H 8.91% N.

EXAMPLE 147

1-(R)-(–)-[4-[3-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl] ethanone fumarate

(A) (R)-(–)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propyl methanesulfonate

To a mixture of (R)-(–)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol (7.26 gm, 24.8 mmoles), triethylamine (3ml, 30 mmoles) in methylene chloride (DCM, 120 ml), methanesulfonyl chloride (3.13 gm, 27.3 moles) was added dropwise at 0° C. The mixture was stirred at room temperature for 1 hr., then concentrated down to a crude mixture. Triethylamine hydrochloride salt was removed by filtration with DCM/ether as solvent. The crude oily mixture was purified with a flash chromatography column (SiO_2, 90 gm; eluted with DCM). The colorless oil, which is the methanesulfonate ester, weighed 6.48 gm (70%), and was used directly in the following step.

(B) 1(R)-(–)-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2methyl-propoxy]-3-ethoxyphenyl]ethanone fumarate

A solution of the above methanesulfonate (6.48 gm, 175 mmoles) in DMF (5 ml) was added in one portion to an aged (½ hr) cold mixture of acetovanillone (4.13 gm, 24.9 moles) and sodium hydride (670 mg, 26.5 moles) in DMF (40 ml) at 0° C. The resulting mixture was warmed to ~50° C. briefly and stirred at room temperature for 16 hrs. The mixture was extracted into DCM (500 ml) and washed twice with water, then brine. The organic solution was dried over $MgSO_4$ and concentrated to an oil. This crude mixture was purified twice by flash chromatography over a silica gel column. The material thus purified weighed 5.37 gm. The fumarate salt was prepared by treatment of purified oil with fumaric acid (1.0 eq.) in ethanol and ether. Slightly off-white crystals were collected: 3.76 gm (38%), m.p.=141°–142° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_4.C_4H_4O_4$ 62.58% C 5.98% H 5.03% N.

Found: 62.52% C 5.75% H 4.96% N.

EXAMPLE 148

3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2,2-dimethyl-1-propanol fumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidine (3.0 gm, 13.6 mmoles), K_2CO_3 (12.5 gm, 17.5 mmoles), 3-bromo-2,2-dimethyl-1-propanol (3 gm, 21 mmoles, 1.5 eq.), tetrabutylammonium hydrogen sulfate (1 gm, phase transfer catalyst) in water (5 ml) and acetonitrile

(150 ml) was heated at reflux for 43 days. TLC showed a small spot for the expected product. The mixture was diluted with EtOAc (400 ml) and washed with brine. The organic solution was dried and concentrated to a dark brown mixture. The crude mixture was purified carefully by flash chromatography (SiO_2, 95 gm to afford the dried pure product; 260 mg, (6%) as an oil. This oil was converted to the fumarate salt by treatment with fumaric acid (98.5 mg, 1.0 eq.) in ethanol. Recrystallization from ethanol:ether yielded 210 mg of white crystals, m.p.=144°–145° C.

ANALYSIS

Calculated for $C_{17}H_{23}FN_2O_2.C_4H_4O_4$: 59.70% C 6.44% H 6.63% N.

Found: 59.52% C 6.38% H 6.52% N.

EXAMPLE 149

1-(S)-(+)1[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl]ethanone fumarate

(A) (S)-(+)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propyl methanesulfonate

To a mixture of (S)-(+)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol (8.8 gm, 30 mmoles), triethylamine (3.2 gm, 32 mmoles) in dichloromethane (DCM, 150 ml), methanesulfonyl chloride (4 gm, 35 mmoles) was added dropwise at 0° C. over 10 minutes. The mixture was stirred at room temperature for 1 hr, then concentrated. Triethylamine HCl salt was filtered off with a little DCM as solvent. The crude oil was purified with a flash chromatography column (SiO_2, 90 gm; eluted with DCM). The colorless oil thus purified weighed 5.28 in (47%) was used immediately in the following step.

(B) 1-(S)-(+)-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-proproxy]-3-methoxyphenyl]ethanone fumarate

A solution of (S)-(+)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl-1-piperidinyl]-2-methyl-1-propyl methanesulfonate (5.28 gm, 14.27 mmoles) in dimethylformamide (DMF, 10 ml) was added in one portion to an aged (1 hr) cold mixture of acetovanillone (3.55 in, 33.1 mmoles) and sodium hydride (530 mg, 22 moles) in DMF (35 ml) at 0° C. under N_2. The reaction was stirred overnight (1.6 hrs.) at room temperature. The mixture was diluted with EtOAc and washed with H_2O (2 times) and brine. The organic solution was dried and concentrated to an oil (9.4 gm). The crude oil mixture was purified by flash chromatography (SiO_2, 60 gm). The oil thus purified weighed 4.3 gm, (68%) and was converted to the fumarate salt (fumaric acid, 1.13 gm) in ethanol. Recrystallization from ethanol gave 1.36 gm of white crystals, m.p.= 163°–165° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2.O_4C_4H_4O_4$ 62.58% C 5.98% H 5.03% N.

Found: 62.40% C 5.84% H 4.92% N.

EXAMPLE 150

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl thioacetate fumarate

To a stirred solution of 0° C. of triphenylphosphine (13.3 g, 0.05 mol) in THF (150 ml), diisopropylazodicarboxylate (10.2 ml, 0.05 mol) was added dropwise. After stirring at 0° C. for 0.5 h, a solution of 6-fluoro-3-[1-(2-hydroxyethyl)-4-piperidinyl]-1,2-benzisoxazole (8.5 g, 0.032 mol) and thioacetic acid (10.2 ml, 0.14 mol) in DMF (35 ml) was added dropwise. The reaction was then stirred at ambient temperature for 16 h, and then it was concentrated at 60° C., under vacuum, to yield a red oil. The oil was tritrated with H_2O, and then it was flash chromatographed on silica gel, eluting first with CH_2Cl_2 and then with 10% MeOH-CH_2Cl_2. The appropriate fractions were concentrated to yield 16.5 g of an oil. The oil was tritrated with Et_2O and the solid (reaction by-products) that formed was removed by filtration. The filtrate was treated with fumaric acid (4.3 g), and 7.2 g of the fumarate salt of the desired product was obtained as an off white solid. The salt was recrystallized from EtOAc and then twice from EtOH to afford 1.0 g (7.0%) of the thioacetate as an off white solid, m.p.=118°–120° C.

EXAMPLE 151

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4,5-dichlorophthalimide

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.83 gm, 10.7 mmol) and 4,5-dichlorophthalic anhydride (2.56 gm, 11.93 mmol, 1.1 eq) in methylene chloride (100 ml, DCM) was stirred for 2 h, white solids precipitated and the TLC showed disappearance of the starting material. The solvent was removed, and the crude solid was loaded onto a flash chromatography column (28 gm, SiO_2, sorbsil C-30, eluted with 1% MeOH in DCM; 0.5% of NH_4OH was added towards the end of elution). The material thus purified weighed 2.26 gm as white crystals. Recrystallization twice from a large volume of hot ethanol (400 ml) yielded 1.57 gm of white shining crystals, m.p.= 132°–134° C.

ANALYSIS

Calculated for $C_{22}H_{18}Cl_2FN_3O_3$: 57.16% C 3.92% H 9.09% N.

Found: 57.13% C 3.63% H 8.93% N.

EXAMPLE 152

N-[2-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]ethyl]phthalimide

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (4.72 g, 0.02 mole), potassium carbonate (4.14 g, 0.03 mole) and N-(2-bromoethyl)phthalimide (6.35 g, 0.0025 mole) in 200 ml of acetonitrile is heated at reflux for 4 hours. The solids are then removed by filtration and the filtrate is concentrated under reduced pressure. The residue is purified by chromatography over silica gel to provide N-[2-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl] ethyl]phthalimide.

EXAMPLE 153

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-3,6-dichlorophthalimide

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.44 gm, 9.24 mmoles) and 3,6-dichlorophthalic anhydride (2.01 gm; 9.27 mmoles) in dichloromethane (DCM, 50 ml) was stirred at room temperature for 1 hr. White precipitates formed and the TLC of the reaction mixture showed that there was no starting amine remaining. The solvent was stripped down and the white solids which were poorly soluble in DCM were loaded onto a flash chromatography column, (SiO_2; 30 gm) and the column was eluted with a solution of 1% CH_3OH in DCM.

The desired product thus obtained weighed 2.29 gm (54%). Recrystallization from hot ethanol yielded 2.15 gm of white crystals, m.p.=163°–164° C.

ANALYSIS

Calculated for $C_{22}H_{18}Cl_2FN_3O_3$: 57.16% C 3.92% H 9.09% N.

Found: 57.16% C 3.64% H 9.13% N.

EXAMPLE 154

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-chlorophthalimide

A stirred mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.63 g, 0.01 mole) and 4-chlorophthalic anhydride (1.82 g, 0.01 mole) in dichloromethane (100 ml) is stirred at room temperature for 3 hours. The solvent is removed under reduced pressure and the residual material is purified by flash chromatography. The product was purified further by recrystallization to give N-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-4-chlorophthalimide.

EXAMPLE 155

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-3-fluorophthalimide

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.37 gm, 8.98 mmoles), 3-fluorophthalic acid (1.82 in, 9.9 moles) and dicyclohexylcarbodiimide (DCC, 5.5 gm, 26.7 mmoles, 2.6 eq) in dichloromethane (DCM, 250 ml) was stirred at room temperature for 18 hrs. The solids were filtered off. The organic solution was concentrated down. The residue was purified on a flash chromatography column (SiO_2, 50 in; eluted with 1% CH_3OH:99% DCM, 1.4 liter; 2–6% CH_3OH:DCM, liter). The desired product thus obtained weighed 2.64 gm (71%) as an off-white solid. Recrystallization from hot ethanol gave 1.41 gm of white crystals, m.p.=142°–143° C.

ANALYSIS

Calculated for $C_{22}H_{19}F_2N_3O_3$: 64.22% C 4.66% H 10.21% N.

Found: 64.11% C 4.70% H 10.14% N.

EXAMPLE 156

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-fluorophthalimide

A stirred mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.63 g, 0.01 mole) and 4-fluorophthalic anhydride (1.83 g, 0.011 mole) in dichloromethane (100 ml) is stirred at room temperature for 4 hours. The solvent is then removed under reduced pressure and the residual solids are purified by flash chromatography. The product is further purified by recrystallization to afford N-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-4-fluorophthalimide.

EXAMPLE 157

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-methylphthalimide

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.44 gm, 9.24 mmoles), 4-methylphthalic anhydride (1.76 gm, 10.8 moles) and dicyclohexylcarbodiimide (2.1 gm, 1.0 moles) in dichloromethane (DCM, 100 ml) was stirred at room temperature for 2 hr. The insolubles were filtered off. The DCM solution was concentrated to a crude solid. This was purified on a flash chromatography column (35 gm, SiO2, Sorbsil-C-30; eluted with 1% CH_3OH in 99% DCM). The material thus purified weighed 1.0 gm (26%) as a white solid. Recrystallization from hot ethanol gave 665 mg of crystals, m.p.= 138°–140° C.

ANALYSIS

Calculated for $C_{23}H_{22}FN_3O_3$: 67.80% C 5.44% H 10.31% N.

Found: 67.67% C 5.48% H 10.30% N.

EXAMPLE 158

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-methoxyphthalimide

A stirred mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.63 g, 0.01 mole) and 4-methoxyphthalic anhydride (1.78 g, 0.01 mole) in dichloromethane (100 ml) is stirred at room temperature for 3 hours. The solvent is then removed under reduced pressure and the residual material is purified by flash chromatography. The product is purified further by recrystallization to give N-[2-[4-(6-fluoro-1,2-benzisoxazol-3yl)-1-piperidinyl] ethyl]-4-methoxyphthalimide.

EXAMPLE 159

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-nitrophthalimide

A stirred mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.63 g, 0.01 mole) and 4-nitrophthalic anhydride (1.93 g, 0.01 mole) in dichloromethane (200 ml) is stirred at room temperature for 3 hours. The solvent is then removed under reduced pressure and the residual material is purified by flash chromatography. The product is purified further by recrystallization to give N-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-nitrophthalimide.

EXAMPLE 160

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-2-hydroxybutane fumarate

To a solution of ethyl 3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propionate (3.21 gm, 10 mmoles) in tetrahydrofuran (THF, 100 ml), methylmagnesium bromide (10 ml, 30 moles, 3M solution in ether) was added dropwise over 15 minutes at room temperature under N_2. The resulting mixture was stirred for 16 hours. The mixture was slowly hydrolyzed with aqueous NH_4Cl solution. The THF solution was diluted with EtOAc (300 ml), then was washed with water and brine. The organic solution was separated and dried over $MgSO_4$. After removal of solvent, the crude product was purified by flash chromatography (25 gm, SiO_2; eluted with 1% CH_3OH:99% DCM). The material thus purified weighed 2.36 gm (77%) as white crystals. This was converted to the fumerate salt by treatment with fumaric acid (895 mg) in ethanol. Recrystallization from ethanol yielded with crystals, 2.47 gm, m.p.=156°–158° C.

ANALYSIS

Calculated for $C_{17}H_{23}FN_2O_2.C_4H_4O_4$: 59.70% C 6.44% H 5.63% N.

Found: 59.40% C 6.27% H 6.28% N.

EXAMPLE 161

Ethyl 3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propionate fumarate

A mixture of 4-(6-fluoro-1,2-benzisoxaxol-3-yl) piperidine (5 gm, 22.7 mmoles), K_2CO_3 (3.8 gm, 27.5

mmoles) and ethyl bromopropionate (5 gm, 27.6 mmoles, 1.2 eq) in acetonitrile (200 ml) was heated at reflux for 16 hours. The mixture was cooled and filtered. The solvent was removed, and the residue was purified on a flash chromatography column (60 gm, SiO_2, eluted with DCM). The material thus purified weighed 7.27 gum (83%). The fumarate salt was prepared by treatment of the free base (2.17 gm) with fumaric acid (820 mg, 1.0 eq) in ethanol. Recrystallization from ethanol yielded 2.49 gm of white crystals, m.p.=135°–136° C.

ANALYSIS

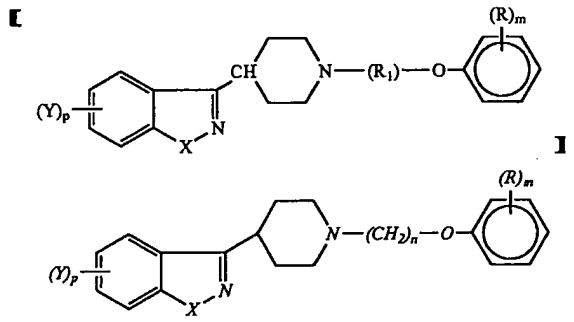
Calculated for $C_{17}H_{21}FN_2O_3.C_4H_4O_4$: 57.79% C 5.77% H 6.42% N.

Founded: 57.86% C 5.67% H 6.30% N.

This invention thus provides a group of chemical compounds that are capable of producing antipsychotic effects and may be capable of affecting negative symptoms of schizophrenia in a beneficial manner. In addition, many of the compounds may also have reduced tendencies to produce extrapyramidal side effects in mammals.

What is claimed is:

1. A compound of the formula:



wherein

X is —O— or —S—;

p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy[, hydroxy and halogen] when p is 2 and X is —O—;

[(R_1) is R_{20}, R_{21}, or R_{22}, wherein:

R_{20} is $—(CH_2)_n—$ where] n is 2, 3, 4 or 5;

[R_{21} is

$—CH_2—CH=CH—CH_2—$,

$—CH_2—C\equiv C—CH_2—$,

$—CH_2—CH=CH—CH_2—CH_2$,

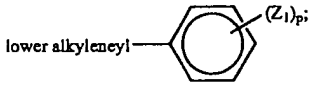
$—CH_2—CH_2—CH=CH—CH_2—$,

$—CH_2—C\equiv C—CH_2—CH_2—$, or

$—CH_2—CH_2—C\equiv C—CH_2—$,

the —CH=CH— bond being cis or trans;

R_{22} is R_{20} or R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one C_1–C_6 linear alkyl group, pheny group or

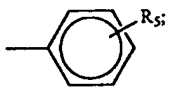


where Z_1 is lower alkyl, —OH, lower alkoxy, $—CF_3$, $—NO_2$, $—NH_2$ or halogen;]

R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, [monoalkylaminocarbonyl, dialkylaminocarbonyl, formyl,] —C(=O)-alkyl, —C(=O)—O-alkyl, —C(=O)-aryl, —C(=O)-heteroaryl, [—CH(OR^7)-alkyl, —C(=W)-alkyl, —C(=W)-aryl, and —C(=W)-heteroaryl;] *or* *—CH(OR_7)-alkyl;*

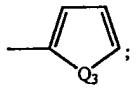
wherein alkyl is lower alkyl;

aryl is phenyl or



wherein R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, [lower dialkylamino,] nitro, cyano, trifluoromethyl, *or* trifluoromethoxy;

heteroaryl is



wherein Q_3 is —O—, —S—, —NH—, *or* —CH=N—;

[W is CH_2 or CHR_8 or $N—R_9$;]

R_7 is hydrogen, lower alkyl, or acyl;

[R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or $—NHR_{10}$; and

R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl, —C(=)-aryl or —C(=O)-heteroaryl,

where aryl and heteroaryl are as defined above;] and

m is 1, 2, or 3;

[all geometric, optical and stereoisomers thereof,] or a pharmaceutically acceptable acid addition salt thereof.

2. A compound as claimed in claim 1, which is 1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

3. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

4. A compound as claimed in claim 1, which is 1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

5. A compound as claimed in claim 1, which is 1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

6. A compound as claimed in claim 1, which is 1-[4-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

7. A compound as claimed in claim 1, which is 1-[4-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

8. A compound as claimed in claim 1, which is 1-[4-[3-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

9. A compound as claimed in claim 1, which is 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-α-methylbenzenemethanol or a pharmaceutically acceptable acid addition salt thereof.

10. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

11. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

12. A compound as claimed as claim 1, which is 1-[4-[4-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperindyl]-butoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

13. A compound as claimed in claim 1, which is 1-[4-[3-[4-(5-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

14. A compound as claimed in claim 1, which is 6-fluoro-3-[1-[1-[3-(2-methoxyphenoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole or a pharmaceutically acceptable acid salt thereof.

15. A compound as claimed in claim 1, which is 1-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyphenyl]phenylmethanone or a pharmaceutically acceptable acid addition salt thereof.

16. A compound as claimed in claim 1, which is 1-[4-[2-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

17. A compound as claimed in claim 1, which is 1-[3-[3-[4-(6-fluoro-1,2-benzisoxzol-3-yl)-1-piperidinyl]-propoxy]phenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

18. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3yl)-1-piperidinyl]-propoxyl]-2-methylphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

19. A compound as claimed in claim 1, which is 1-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-5-methylphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

20. A compound as claimed in claim 1, which is N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyphenyl]acetamide or a pharmaceutically acceptable acid addition salt thereof.

21. A compound as claimed in claim 1, which is 1-(4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methylphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

22. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]phenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

23. A compound as claimed in claim 1, which is 4-[3-[4-(6-fluoro-1,2-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzonitrile or a pharmaceutically acceptable acid addition salt thereof.

24. A compound as claimed in claim 1, which is 1-[3,5-dibromo-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

25. A compound as claimed in claim 1, which is 6-fluoro-3-[1-(3-phenoxypropyl)-4-piperidinyl]-1,2-benzisoxazole or a pharmaceutically acceptable acid addition salt thereof.

26. A compound as claimed in claim 1, which is [1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl]-1-piperidinyl]-propoxy]-3-methylmercaptophenyl]ethanone] *1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methylmercaptophenyl]ethanone* or a pharmaceutically acceptable acid addition salt thereof.

27. A compound as claimed in claim 1, which is 1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

28. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]phenylmethanone or a pharmaceutically acceptable acid addition salt thereof.

29. A compound as claimed in claim 1, which is 3-[1-[3-[4-ethoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole or a pharmaceutically acceptable acid addition salt thereof.

30. A compound as claimed in claim 1, which is 3-[1-[3-[4-(1-acetoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole or a pharmaceutically acceptable acid addition salt thereof.

31. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]pentanone or a pharmaceutically acceptable acid addition salt thereof.

32. A compound as claimed in claim 1, which is 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-N-methylbenzeneamine or a pharmaceutically acceptable acid addition salt thereof.

33. A compound as claimed in claim 1, which is 3-[1-[3-(4-bromo-2-methoxyphenoxy)propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole or a pharmaceutically acceptable acid addition salt thereof.

34. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]propanone or a pharmaceutically acceptable acid addition salt thereof.

35. A compound as claimed in claim 1, which is 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzamide or a pharmaceutically acceptable acid addition salt thereof.

36. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-(methylamino)phenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

37. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-ethoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

38. A compound as claimed in claim 1, which is N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]phenyl]acetamide, or a pharmaceutically acceptable acid addition salt thereof.

39. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-dimethylaminophenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

40. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-2-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

41. A compound as claimed in claim 1, which is 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxy-α-methylbenzene methanol, or a pharmaceutically acceptable acid addition salt thereof.

42. A compound as claimed in claim 1, which is 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline, or a pharmaceutically acceptable acid addition salt thereof.

43. A compound as claimed in claim 1, which is N-[5-acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide, or a pharmaceutically acceptable acid addition salt thereof.

44. A compound as claimed in claim 1, which is 3-[1-[3-(4-ethyl-2-methoxyphenoxy)propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole, or a pharmaceutically acceptable acid addition salt thereof.

45. A compound as claimed in claim 1, which is 1-[3,5-dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

46. A compound as claimed in claim 1, which is N-[3-[3-[4-(6-fluoro-1,2-benzisoxaxol-3-yl)-1-piperidinyl]-propoxy]phenyl]acetamide, or a pharmaceutically acceptable acid addition salt thereof.

47. A compound as claimed in claim 1, which is 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy] aniline, or a pharmaceutically acceptable acid addition salt thereof.

48. A compound as claimed in claim 1, which is 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyaniline, or a pharmaceutically acceptable acid addition salt thereof.

49. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methylaminophenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

50. A compound as claimed in claim 1, which is N-[3-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyphenyl]acetamide, or a pharmaceutically acceptable acid addition salt thereof.

51. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

52. A compound as claimed in claim [1] *132*, which is N,N-dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide, or a pharmaceutically acceptable acid addition salt thereof.

53. A compound as claimed in claim [1] *132*, which is 1-[4-[3-[4(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-(methylamino)phenyl]ethanone oxime, or a pharmaceutically acceptable acid addition salt thereof.

54. A compound as claimed in claim [1] *132*, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]methoxyphenyl]ethanone oxime O-methyl ether, or a pharmaceutically acceptable acid addition salt thereof.

55. A compound as claimed in claim [1] *132*, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone hydrazone, or a pharmaceutically acceptable acid addition salt thereof.

56. A compound as claimed in claim [1] *132*, which is 6-fluoro-3-[1-[3-[2-methoxy-4-(1-methylethenyl)phenoxy] propyl]-4-piperidinyl]-1,2-benzisoxazole, or a pharmaceutically acceptable acid addition salt thereof.

57. A compound as claimed in claim [1] *87*, which is (Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2butenyl]oxy]-3-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

58. A compound as claimed in claim [1] *87*, which is (E)-1-[3-[4-[[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-hydroxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

59. A compound [as claimed in claim 1], which is (E)-1-[3-[4-[[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2butenyl]oxy]-4-benzyloxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

60. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-bromophenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

61. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]-2,2,2-trifluoroethanone, or a pharmaceutically acceptable acid addition salt thereof.

62. A compound as claimed in claim 1, which is 3-[1-[3-[4-(1-methoxyethyl)-2-hydroxyphenoxyl]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole, or a pharmaceutically acceptable acid addition salt thereof.

63. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisothazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

64. A compound as claimed in claim 1, which is 4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxy-alpha-methylbenzenemethanol, or a pharmaceutically acceptable acid addition salt thereof.

65. A compound as claimed in claim [1, which is 1-(R)-(–)-[4-[3-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl]ethanone, or] *104, which is 1-(R)-(–)-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl] ethanone, or* a pharmaceutically acceptable acid addition salt thereof.

66. A compound as claimed in claim [1] *104*, which is 1-(S)-(+)-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl] ethanone, or a pharmaceutically acceptable acid addition salt thereof.

67. The compound of claim 1, wherein the pharmaceutically acceptable addition salt is selected from the group consisting of salts of mineral acids, salts of monobasic carboxylic acids, slats of dibasic carboxylic acids, and salts of tribasic carboxylic acids.

68. The compound of claim 67, wherein said pharmaceutically acceptable addition salts are selected from the group consisting of salts of hydrochloric acid, sulfuric acid, nitric acid, acetic acid, propionic acid, maleic acid, fumaric acid, carboxysuccinic acid, and citric acid.

69. The compound of claim 1, wherein Y is in the 5 position.

70. The compound of claim 1, wherein Y is in the 6 position.

71. The compound of claim 1, wherein Y is selected from the group consisting of hydrogen, chlorine, bromine and fluorine.

72. The compound of claim 71, wherein Y is fluorine.

73. The compound of claim 72, wherein Y is in the 6 position.

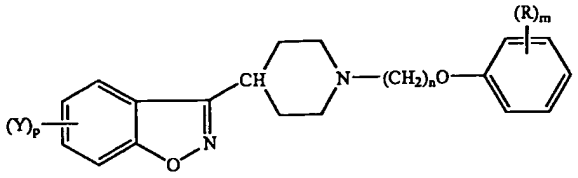
74. The compound of claim 1, wherein p is 2, X is —O—, and Y is [selected from the group consisting of] lower alkoxy[, hydroxy and halogen groups].

75. The compound of claim 74, wherein Y is a methoxy group.

[76. The compound of claim 1, wherein R_1 is —CH_2—CH=CH—CH_2—.]

77. The compound of claim 1, wherein R is selected from the group consisting of hydrogen, C_1–C_3 alkyl, C_1–C_3alkoxy, hydroxyl, —$COCF_3$, C_1–C_6alkanoyl, Cl, F, Br, I, C_1–C_3 alkylamino, [—NO_3,] —NO_2, —CF_3, —OCF_3, and —C(=O)-lower alkyl.

78. A compound of the formula:



wherein p is 1 or 2;

Y is hydrogen, Cl, Br, or F, when p is 1;

Y is lower alkoxy, [hydroxy, or halogen] when p is 2;

n is 2, 3, or 4;

R is hydrogen, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl, [alkanoyl,] Cl, F, Br, I, amino, C_1–C_3 mono or dialkyl amino, acylamino, —NO_2, —OCF_3, —CF_3, alkyl-C(=O)—, CF_3—C(=O)—, or —CH(OR_7)-alkyl;

alkyl is lower alkyl

R_7 is hydrogen, lower alkyl-C(=O)—, or CF_3—C(=O)—;

and m is 1, 2, or 3;

R is hydrogen, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl, [alkanoyl,] Cl, F, Br, I, amino, C_1–C_3 mono or dialkyl amino, acylamino, —NO_2, —OCF_3, —CF_3, alkyl-C(=O)—, CF_3—C(=O)—, or —CH(OR_7)-alkyl;

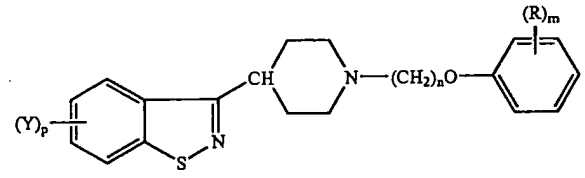
alkyl is lower alkyl;

R_7 is hydrogen, lower alkyl, lower alkyl-C(=O)—, or CF_3—C(=O)—;

and m is 1, 2, or 3;

all geometric, optical and stereoisomers thereof or a pharmaceutically acceptable acid addition salt thereof.

79. A compound of the formula:



wherein p is 1 or 2;

Y is hydrogen, Cl, Br, or F, when p is 1;

Y is lower alkoxy, [hydroxy, or halogen] when p is 2;

n is 2, 3, or 4;

R is hydrogen, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl, acyl, alkanoyl, Cl, F, Br, I, amino, C_1–C_3 mono or dialkyl amino, acylamino, —NO_2, —OCF_3, —CF_3, alkyl-C(=O)—, CF_3—C(=O)—, or —CH(OR_7)-alkyl;

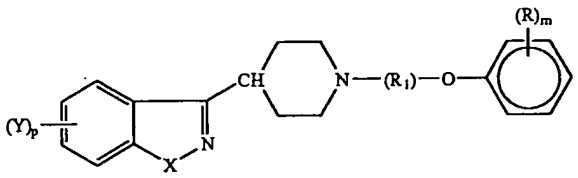
alkyl is lower alkyl;

R_7 is hydrogen lower alkyl, [or] lower alkyl-C(=O)—, *or* CF_3—C(=O)—;

and m is 1, 2, or 3;

all geometric, optical and stereoisomers thereof or a pharmaceutically acceptable acid addition salt thereof.

80. A compound [of the formula:



wherein

X is —O— or —S—;

p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—,

(R_1) is R_{20}, R_{21}, or R_{22}, wherein:

R_{20}

R_{21} is

—CH_2 —CH=CH—CH_2—,

—CH_2—C≡C—CH_2—,

—CH_2—CH=CH—CH_2—CH_2 —,

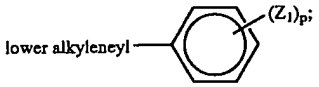
—CH_2—CH_2—CH=CH—CH_2—,

—CH_2—CH≡C—CH_2—CH_2—, or

—CH_2—CH_2—C≡C—CH_2—,

the —CH=CH— bond being cis or trans;

R_{22} is R_{20} is R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one C_1–C_6 linear alkyl group, phenyl group or



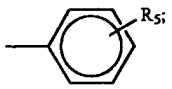
wherein Z_1 is lower alkyl, —OH, lower alkoxy, —CF_3, —NO_2, —NH_2 or halogen; and R and m are as defined hereinafter;

m is 1, 2, or 3; and

when m is 1, 2, or 3, R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, formyl, —C(=O)-alkyl, —C(=O)—O-alkyl, —C(=O)-aryl, —C(=O)-heteroaryl, —CH(OR^7)-alkyl, —C(=W)-alkyl, —C(=W)-aryl, and —C(=W)-heteroaryl;

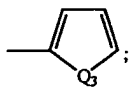
alkyl is lower alkyl;

aryl is phenyl or



where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;

heteroaryl is



Q_3 is —O—, —S—, —NH—, —CH=N—;

W is CH_2 or CHR_8 or N—R_9;

R_7 is hydrogen, lower alkyl, or acyl;

R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and

R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl, —C(=O)-aryl or —C(=O)-heteroaryl,

where aryl and heteroaryl are as defined above; and] *as claimed in claim 1 with the proviso that* when m is 3, R is not —C(=O)-heteroaryl or —C(=W)-heteroaryl;

[all geometric, optical and stereoisomers thereof,] or *a* pharmaceutically acceptable acid addition salt thereof.

81. A compound as claimed in claim **[1]** *87*, which is (E)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

82. A pharmaceutical composition, which comprises *a* compound as claimed in any one of claims **[1–81]** *1–75 and 77–81*, and a pharmaceutically acceptable carrier therefor.

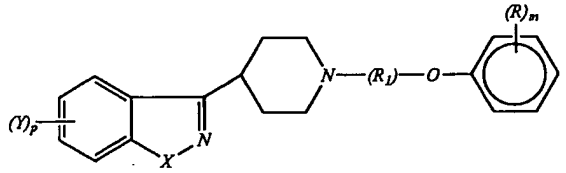
83. An antipsychotic composition which comprises a compound as claimed in any one of claims **[1–81]** *1–75 and 77–81*, in an amount sufficient to produce an antipsychotic effect, and a pharmaceutically acceptable carrier therefor.

84. A method of treating psychoses, which comprises administering to a mammal a psychoses-treating effective amount of a compound as claimed in any one of claims **[1–81]** *1–75 and 77–81*.

85. An analgesic composition which comprises a compound as claimed in any one of claims **[1–81]** *1–75 and 77–81*, in an amount sufficient to produce a pain-relieving effect, and a pharmaceutically acceptable carrier therefor.

86. A method of alleviating pain, which comprises administering to a mammal a pain-relieving effective amount of a compound as claimed in any one of claims **[1–81]** *1–75 and 77–81*.

87. A compound of the formula



wherein

X is —O— or —S—;

p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy, hydroxy and halogen, when p is 2 and X is —O—;

(R_1) *is*

—CH_2—CH=CH—CH_2—,

—CH_2—C≡C—CH_2—,

—CH_2—CH=CH—CH_2—CH_2—,

—CH_2—CH_2 —CH=CH—CH_2—,

—CH_2—C≡C—CH_2 —CH_2—, *or*

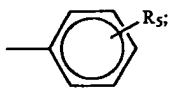
—CH_2—CH_2—C≡C—CH_2—,

the —CH=CH— bond being cis or trans;

R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, dialkylaminocarbonyl, formyl, —C(=O)-alkyl, —C(=O)—O-alkyl, —C(=O)-aryl, —C(=O)-heteroaryl, —CH(OR_7)-alkyl, —C(=W)-alkyl, —C(=W)-aryl, or —C(=W)-heteroaryl;

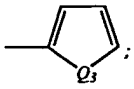
wherein alkyl is lower alkyl;

aryl is phenyl or



wherein R_3 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, or trifluoromethoxy;

heteroaryl is



wherein Q_3 is —O—, —S—, —NH—, or —CH=N—;

W is CH_2 or CHR_8 or N—R_9;

R_7 is hydrogen, lower alkyl, or acyl;

R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and

R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl aryl, —C(=O)-aryl, or —C(=O)-heteroaryl, wherein aryl and heteroaryl are as defined above; and

m is 1, 2, or 3;

all geometric, optical and stereoisomers thereof, or a pharmaceutically acceptable acid addition salt thereof.

88. The compound of claim 87, wherein the pharmaceutically acceptable addition salt is selected from the group consisting of salts of minerals acids, salts of monobasic carboxylic acids, salts of dibasic carboxylic acids, and salts of tribasic carboxylic acids.

89. The compound of claim 88, wherein said pharmaceutically acceptable addition salts are selected from the group consisting of salts of hydrochloric acid, sulfuric acid, nitric acid acetic acid, propionic acid, maleic acid, fumaric acid, carboxysuccinic acid, and citric acid.

90. The compound of claim 87, wherein Y is in the 5 position.

91. The compound of claim 87, wherein Y is in the 6 position.

92. The compound of claim 87, wherein Y is selected from the group consisting of hydrogen, chlorine, bromine and fluorine.

93. The compound of claim 92, wherein Y is fluorine.

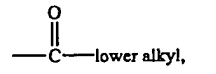
94. The compound of claim 93, wherein Y is in the 6 position.

95. The compound of claim 87, wherein p is 2, X is —O—, and Y is selected from the group consisting of lower alkoxy, hydroxy, and halogen groups.

96. The compound of claim 95, wherein Y is a methoxy group.

97. The compound of claim 87, wherein R_7 is $—CH_2—CH=CH—CH_2$.

98. The compound of claim 87, wherein R is selected from the group consisting of hydrogen, $C_1—C_3$ alkyl, $C_1—C_3$ alkoxy, hydroxyl, $—COCF_2$, $C_1–C_6$ alkanoyl, Cl, F, Br, I, $C_1–C_3$ alkylamino, $—NO_2$, $—CF_3$, $—OCF_2$, and alkylamino,



99. A pharmaceutical composition, which comprises a compound as claimed in claim 87, and a pharmaceutically acceptable carrier therefor.

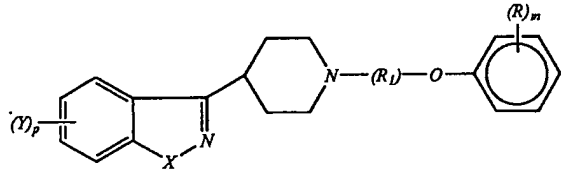
100. An antipsychotic composition which comprises a compond as claimed in claim 87, in an amount sufficient to produce an antipsychotic effect, and a pharmaceutically acceptable carrier therefor.

101. A method of treating psychoses, which comprises administering to a mammal a psychoses-treating effective amount of a compound as claimed in claim 87.

102. An analgesic composition which comprises a compound as claimed in claim 87, in an amount sufficient to produce a pain-relieving effect, and a pharmaceutically acceptable carrier therefor.

103. A method of alleviating pain, which comprises administering to a mammal a pain-relieving effective amount of a compound as claimed in claim 87.

104. A compound of the formula



wherein

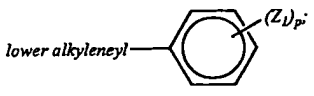
X is —O— or —S—;

p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy, hydroxy, or halogen when p is 2 and X is —O—;

(R_1) is R_{20} or R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one $C_1–C_6$ linear alkyl group, phenyl group or



wherein Z_1 is lower alkyl, —OH, lower alkoxy, $—CF_3$, $—NO_2$, $—NH_2$, or halogen.

105. The compound of claim 104, wherein the pharmaceutically acceptable addition salt is selected from the group consisting of salts of mineral acids, salts of monobasic carboxylic acids, salts of dibasic carboxylic acids, and salts of tribasic carboxylic acids.

106. The compound of claim 105, wherein said pharmaceutically acceptable addition salts are selected from the group consisting of salts of hydrochloric acid, sulfuric acid, nitric acid, acetic acid, propionic acid, maleic acid, fumaric acid, carboxysuccinic acid, and citric acid.

107. The compound of claim 104, wherein Y is in the 5 position.

108. The compound of claim 104, wherein Y is in the 6 position.

109. The compound of claim 104, wherein Y is selected from the group consisting of hydrogen, chlorine, bromine and fluorine.

110. The compound of claim 109, wherein Y is fluorine.

111. The compound of claim 110, wherein Y is in the 6 position.

112. The compound of claim 104, wherein p is 2, X is —O—, and Y is selected from the group consisting of lower alkoxy, hydroxy and halogen groups.

113. The compound of claim 112, wherein Y is a methoxy group.

114. The compound of claim 104, wherein R is selected from the group consisting of hydrogen, $C_1–C_3$ alkyl, $C_1–C_3$ alkoxy, hydroxyl, $—COCF_3$, $C_1–C_6$ alkanoyl, Cl, F, Br, I, $C_1–C_3$ alkylamino,

$—NO_2$, $—CF_3$, $—OCF_3$, and 

115. A pharmaceutical composition, which comprises a compound as claimed in claim 104, and pharmaceutically acceptable carrier therefor.

116. A antipsychotic composition which comprises a compound as claimed in claim 104, in an amount sufficient to produce an antipsychotic effect, and a pharmaceutically acceptable carrier therefor.

117. A method of treating psychoses, which comprises administering to a mammal a psychoses-treating effective amount of a compound as claimed in claim 104.

118. An analgesic composition which comprises a compound as claimed in claim 104, in an amount sufficient to produce a pain-relieving effect, and a pharmaceutically acceptable carrier therefor.

119. A method of alleviating pain, which comprises administering to a mammal a pain-relieving effective amount of a compound as claimed in claim 104.

120. A compound as claimed in claim 87, with the proviso that when m is 3, R is not —C(=O)-aryl, or —C(=O)-heteroaryl, all geometric, optical and stereoisomers thereof, or a pharmaceutically acceptable acid addition salt thereof.

121. A pharmaceutically composition, which comprises a compound as claimed in claim 120, and a pharmaceutically acceptable carrier therefor.

122. An antipsychotic composition which comprises a compound as claimed in claim 120, in an amount sufficient to produce an antipsychotic effect, and a pharmaceutically acceptable carrier therefor.

123. A method of treating psychoses, which comprises administering to a mammal a psychoses-treating effective amount of a compound as claimed in claim 120.

124. An analgesic composition which comprises a compound as claimed in claim 120, in an amount sufficient to produce a pain-relieving effect, and a pharmaceutically acceptable carrier therefor.

125. A method of alleviating pain, which comprises administering to a mammal a pain-relieving effective amount of a compound as claimed in claim 120.

126. A compound as claimed in claim 104, with the proviso that when m is 3, R is not —C(=O)-aryl, or —C(=O)-heteroaryl, all geometric, optical and stereoiso-

mers thereof, or a pharmaceutically acceptable acid addition salt thereof.

127. A pharmaceutical composition, which comprises a compound as claimed in claim 126, and a pharmaceutically acceptable carrier therefor.

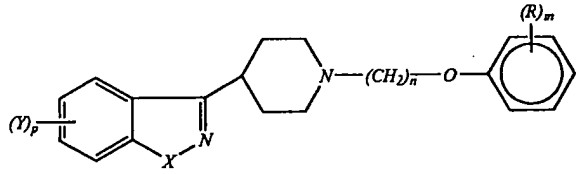
128. An antipsychotic composition which comprises a compound as claimed in claim 126, in an amount sufficient to produce an antipsychotic effect, and a pharmaceutically acceptable carrier therefor.

129. A method of treating psychoses, which comprises administering to a mammal a psychoses-treating effective amount of a compound as claimed in claim 126.

130. An analgesic composition which comprises a compound as claimed in claim 126, in an amount sufficient to produce a pain-relieving effect, and a pharmaceutically acceptable carrier therefor.

131. A method of alleviating pain, which comprises administering to a mammal a pain-relieving effective amount of a compound as claimed in claim 126.

132. A compound of formula



wherein

X is —O— or —S—;

p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

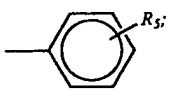
Y is lower alkoxy, hydroxy or halogen when p is 2 and X is —O—;

n is 2, 3, 4 or 5;

R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, dialkylaminocarbonyl, formyl, —C(=O)-alkyl, —C(=O)-O-alkyl, —C(=O)-aryl, —C(=O)-heteroaryl, —CH(OR$_7$)-alkyl, —C(=W)-alkyl, —C(=W)-aryl, or —C(=W)-heteroaryl;

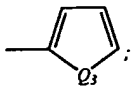
wherein alkyl is lower alkyl;

aryl is phenyl or



wherein R$_5$ is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, nitro, cyano, trifluoromethyl, or trifluoromethoxy;

heteroaryl is



wherein Q$_3$ is —O—, —S—, —NH—, or —CH=N—;

W is CH$_2$ or CHR$_8$ or N—R$_9$;

R$_7$ is hydrogen, lower alkyl, or acyl;

R$_8$ is lower alkyl;

R$_9$ is hydroxy, lower alkoxy, or —NHR$_{10}$; and

R$_{10}$ is hydrogen, lower alkyl, C$_1$–C$_3$ acyl, aryl, —C(=O)-aryl or —C(=O)-heteroaryl;

wherein aryl and heteroaryl are as defined above; and

m is 1, 2, or 3;

with the proviso that at least one R is selected from the group consisting of dialkylaminocarbonyl, formyl, —C(=W)-alkyl, —C(=W)-aryl, and —C(=W)-heteroaryl;

all geometric, optical and stereoisomers thereof, or a pharmaceutically acceptable acid addition salt thereof.

133. The compound of claim 132, wherein the pharmaceutically acceptable addition salt is selected from the group consisting of salts of mineral acids, salts of monobasic carboxylic acids, salts of dibasic carboxylic acids, and salts of tribasic carboxylic acids.

134. The compound of claim 133, wherein said pharmaceutically acceptable addition salts are selected from the group consisting of salts of hydrochloric acid, sulfuric acid, nitric acid, acetic acid, propionic acid, maleic acid, furmaric acid, carboxysuccinic acid, and citric acid.

135. The compound of claim 132, wherein Y is in the 5 position.

136. The compound of claim 132, wherein Y is in the 6 position.

137. The compound of claim 132, wherein Y is selected from the group consisting of hydrogen, chlorine, bromine and fluorine.

138. The compound of claim 137, wherein Y is fluorine.

139. The compound of claim 138, wherein Y is in the 6 position.

140. The compound of claim 132, wherein p is 2, X is —O—, and Y is selected from the group consisting of lower alkoxy, hydroxy and halogen groups.

141. The compond of claim 140, wherein Y is a methoxy group.

142. The compound of claim 132, wherein one R group is selected from the group consisting of hydrogen, C$_1$–C$_3$ alkyl, C$_1$–C$_3$ alkoxy, hydroxyl, —COCF$_3$, C$_1$–C$_6$ alkanoyl, Cl, F, Br,I, C$_1$–C$_3$ alkylamino,

—NO$_2$, —CF$_3$, —OCF$_3$, and —C(=O)-lower alkyl.

143. A pharmaceutical composition, which comprises a compound as claimed in claim 132, and a pharmaceutical acceptable carrier therefor.

144. An antipsychotic composition which comprises a compound as claimed in claim 132, in an amount sufficient

to produce an antipsychotic effect, and a pharmaceutically acceptable carrier therefor.

145. A method of treating psychoses, which comprises administering to a mammal a psychoses-treating effective amount of a compound as claimed in claim 132.

146. An analgesic composition which comprises a compound as claimed in claim 132, in an amount sufficient to produce a pain-relieving effect, and a pharmaceutically acceptable carrier therefor.

147. A method of alleviating pain, which comprises administering to a mammal a pain-relieving effective amount of a compound as claimed in claim 132.

* * * * *

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 5

Patent #: 5364866 **Issue Dt:** 11/15/1994 **Application #:** 07969383 **Filing Dt:** 10/30/1992

Inventors: JOSEPH T. STRUPCZEWSKI, GROVER C. HELSLEY, YULIN CHIANG, KENNETH J. BORDEAU et al

Title: HETEROARYLPIPERIDINES, PYRROLIDINES AND PIPERAZINES AND THEIR USE AS ANTIPSYCHOTICS AND ANALETICS

Assignment: 1

Reel/Frame: 006437/0333 **Recorded:** 02/17/1993 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST.

Assignors: STRUPCZEWSKI, JOSEPH T. **Exec Dt:** 01/28/1993

HELSLEY, GROVER C. **Exec Dt:** 01/29/1993

CHIANG, YULIN **Exec Dt:** 01/28/1993

BORDEAU, KENNETH J. **Exec Dt:** 01/28/1993

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1300 I STREET, N.W.
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Assignment: 2

Reel/Frame: 010452/0703 **Recorded:** 12/14/1999 **Pages:** 5

Conveyance: MERGER AND CHANGE OF NAME

Assignor: HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED **Exec Dt:** 12/22/1995

Assignee: HOECHST MARION ROUSSEL, INC.
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LARA C. KELLEY
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Assignment: 3

Reel/Frame: 010567/0944 **Recorded:** 02/08/2000 **Pages:** 4

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: HOECHST MARION ROUSSEL, INC. **Exec Dt:** 12/15/1999

Assignee: AVENTIS PHARMACEUTICALS INC.
10236 MARION PARK DRIVE
KANSAS CITY, MISSOURI 64137

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Assignment: 4

Reel/Frame: 020119/0606 **Recorded:** 11/16/2007 **Pages:** 8

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: AVENTIS PHARMACEUTICALS INC. **Exec Dt:** 12/28/2001

Assignee: HMR PHARMA INC.
10236 MARION PARK DRIVE
KANSAS CITY, MISSOURI 10236

Correspondent: RAYMOND S. PARKER
1041 ROUTE 202-206
BRIDGEWATER, NJ 08807

Assignment: 5

Reel/Frame: 020174/0006 **Recorded:** 11/29/2007 **Pages:** 8

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: HMR PHARMA INC. **Exec Dt:** 12/28/2001

Assignee: AVENTIS HOLDINGS INC.
3711 KENNETT PIKE
GREENVILLE, DELAWARE 19807

Correspondent: RAYMOND S. PARKER
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Web interface last modified: October 18, 2008 v.2.0.2

EXHIBIT 3

US005364866A

United States Patent [19]

Strupczewski et al.

[11] **Patent Number: 5,364,866**

[45] **Date of Patent: Nov. 15, 1994**

[54] **HETEROARYLPIPERIDINES, PYRROLIDINES AND PIPERAZINES AND THEIR USE AS ANTIPSYCHOTICS AND ANALETICS**

[75] Inventors: **Joseph T. Strupczewski**, Flemington; **Grover C. Helsley**, Stockton; **Yulin Chiang**, Convent Station, all of N.J.; **Kenneth J. Bordeau**, Upper Black Eddy, Pa.; **Edward J. Glamkowski**, Warren, N.J.

[73] Assignee: **Hoechst-Roussel Pharmaceuticals, Inc.**, Somerville, N.J.

[21] Appl. No.: **969,383**

[22] Filed: **Oct. 30, 1992**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 788,269, Nov. 5, 1991, abandoned, which is a continuation-in-part of Ser. No. 944,705, Sep. 5, 1991, abandoned, which is a continuation of Ser. No. 619,825, Nov. 29, 1990, abandoned, which is a continuation of Ser. No. 456,790, Dec. 29, 1989, abandoned, which is a continuation-in-part of Ser. No. 354,411, May 19, 1989, abandoned.

[51] **Int. Cl.**[5] **A61K 31/445**; A61K 31/495; A61K 31/42; C07D 211/00

[52] **U.S. Cl.** **514/321**; 514/254; 514/318; 514/322; 514/373; 514/379; 514/403; 544/257; 544/366; 544/368; 546/194; 546/198; 546/199; 546/270; 546/271; 548/207; 548/356.5

[58] **Field of Search** 546/194, 198, 199; 514/318, 321, 322

[56] **References Cited**

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Primary Examiner—Cecilia Tsang
Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner

[57] **ABSTRACT**

Heteroarylpiperidines, pyrrolidines, and piperazines are useful as antipsychotic and analgesic agents. The compounds are especially useful for treating psychoses by administering to a mammal a psychoses-treating effective amount of one of the compounds. The compounds are also useful as analgesics by administering a pain-relieving effective amount of one of the compounds to a mammal.

86 Claims, No Drawings

HETEROARYLPIPERIDINES, PYRROLIDINES AND PIPERAZINES AND THEIR USE AS ANTIPSYCHOTICS AND ANALETICS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of application Ser. No. 788,269, filed Nov. 5, 1991 (Attorney Docket No. 02489-0028-03000), now abandoned, which is a continuation-in-part of application Ser. No. 944,705, filed Sep. 5, 1991 (Attorney Docket No. 02489-0028-04000), now abandoned, which is a continuation of application Ser. No. 619,825, filed Nov. 29, 1990 (Attorney Docket No. 02489-0028-02000), now abandoned, which is a continuation of application Ser. No. 456,790, filed Dec. 29, 1989 (Attorney Docket No. 02489-0028-01000), now abandoned, which is a continuation-in-part of application Ser. No. 354,411, filed May 19, 1989, (Attorney Docket Nos. 02489-0028-00000 and HR-1161), now abandoned. The entire disclosure of these applications is relied upon and incorporated by reference herein.

BACKGROUND OF THE INVENTION

This invention relates to heteroarylpiperidines, pyrrolidines and piperazines. More particularly, this invention relates to heteroarylpiperidines, pyrrolidines and piperazines having antipsychotic activity and to their use as antipsychotic drugs.

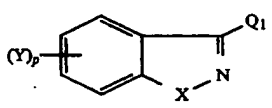
The therapeutic treatment of schizophrenic patients by administration of neuroleptic drugs, such as chlorpromazine, haloperidol, sulpiride, and chemically closely related compounds, is widespread. While control of schizophrenic symptoms has been successful, treatment with these drugs does not cure the psychotic patient, who will almost certainly relapse if medication is discontinued. There exists a continuing need in the art for antipsychotic drugs for the treatment of psychoses.

Moreover, some of the known neuroleptics produce unwanted side effects. For example, the side effects of many antipsychotic drugs include the so-called extrapyramidal symptoms, such as rigidity and tremor, continuous restless walking, and tardive dyskinesia which causes facial grimacing, and involuntary movements of the face and extremities. Orthostatic hypotension is also common. Thus, there also exists a need in the art for antipsychotic drugs that produce fewer or less severe manifestations of these common side effects.

Moreover, there has been a need for drugs that can produce other biological effects. For example, relief from pain has been an age-old aspiration which has led to the discovery of natural and synthetic analgetics. Nevertheless, the need for safe and effective analgetics has continued to the present day.

SUMMARY OF THE INVENTION

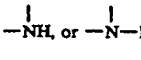
This invention aids in fulfilling these needs in the by providing a compound of the formula:



(I)

wherein

X is —O—, —S—,



—NH, or —N—R2;

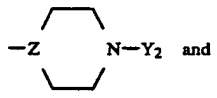
R_2 is selected from the group consisting of lower alkyl, aryl lower alkyl, aryl, cycloalkyl, aroyl, alkanoyl, and phenylsulfonyl groups;

p is 1 or 2;

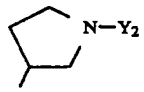
Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—;

Q_1 is selected from the group consisting of:

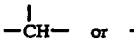


(a) and



(b)

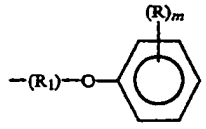
where Z is



—CH— or —N—;

and

Y_2 is selected from the group consisting of:



(1)

in which (R_1) is $—(CH_2)_n—$ where n is 2, 3, 4, or 5; or

—CH2—CH≡CH—CH2—,

—CH2—C≡C—CH2—,

—CH2—CH=CH—CH2—CH2—,

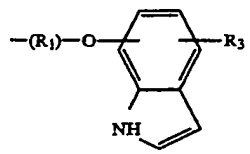
—CH2—CH2—CH=CH—CH2—,

—CH2—C≡C—CH2—CH2—, or

—CH2—CH2—C≡C—CH2—,

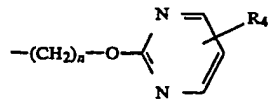
the —CH=CH— bond being cis or trans; and

R and m are as defined hereinafter;



(2)

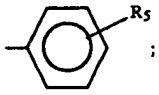
where R_3 is H or $—OCH_3$ and n has the above meaning;



(3)

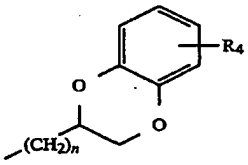
R_4 is hydrogen, lower alkyl, lower alkoxy, amino, mono- or dialkylamino, C_1–C_3 acyl amino, C_1–C_6 alkanoyl, trifluoromethyl, chlorine, fluorine, bromine,

in which aryl is phenyl or



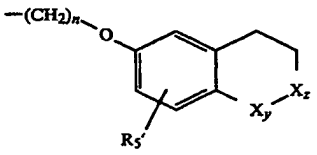
where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;
where n has the above meaning;

(4)



where n and R_4 are as previously defined;

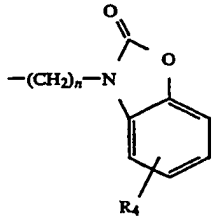
(5)



where either one of X_y or X_z is

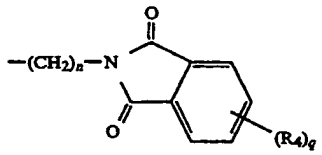
and the other is —CH_2—;
and
R_5' is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, or bromine; and

(6)



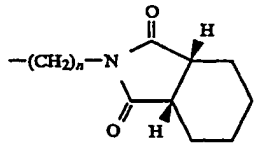
where n and R_4 are as previously defined;

(7)



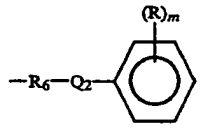
where n and R_4 are as previously defined;

(8)

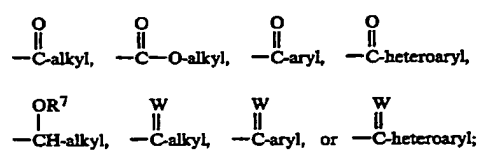


where n is as previously defined;

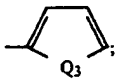
(9)



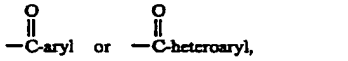
where Q_2 is S, NH, or —CH_2—;
R_6 is the same as R_1 when Q_2 is S or NH; and
when Q_2 is —CH_2—, R_6 is selected from the group consisting of:
—CH_2—CH_2—
—CH_2—CH_2—CH_2—
—CH_2—CH_2—CH_2—CH_2—
—CH_2—CH=CH_2—CH_2—
—CH_2—CH_2—CH=CH—
—CH_2—CH=CH—CH_2—
—CH_2—CH_2—CH=CH—
—CH_2—CH=CH—CH_2—CH_2—
—CH_2—CH_2—CH=CH—CH_2—
—CH_2—CH_2—CH_2—CH=CH—
—CH_2—CH=CH—CH_2—CH_2—
—CH_2—CH_2—CH=CH—CH_2—
—CH_2—CH_2—CH_2—CH=CH—
—CH_2—C≡C—CH_2
—CH_2—CH_2—C≡C—
—CH_2—C≡C—CH_2—CH_2—
—CH_2—CH_2—C≡C—CH_2—
—CH_2—CH_2—CH_2—CH_2≡C—
the —CH=CH— bond being cis or trans;
R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, dialkylaminocarbonyl, formyl,



alkyl is lower alkyl;
aryl is as previously defined;
heteroaryl is

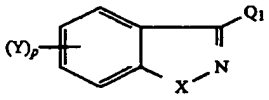


Q_3 is —O—, —S—, —NH, —CH=N;
W is CH_2 or CHR_8 or N—R_9;
R_7 is hydrogen, lower alkyl, or acyl;
R_8 is lower alkyl;
R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and
R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,



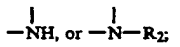
where aryl and heteroaryl are as defined above; and
m is 1, 2, or 3;
or a pharmaceutically acceptable acid addition salt thereof.

This invention also aids in fulfilling these needs the art by providing a compound of the formula:

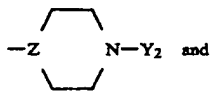


(I)

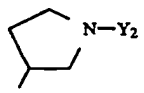
wherein
X is —O—, —S—,



R_2 is selected from the group consisting of lower alkyl, aryl lower alkyl, aryl, cycloalkyl, aroyl, alkanoyl, and phenylsulfonyl groups;
p is 1 or 2;
Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;
Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—;
Q_1 is selected from the group consisting of:

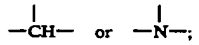


(a)

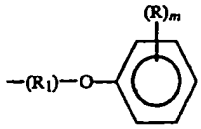


(b)

where Z is

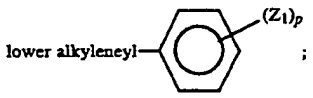


and
Y_2 is selected from the group consisting of:

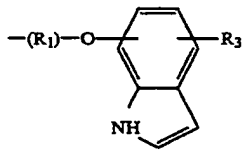


(1)

in which (R_1) is R_{20}, R_{21} or R_{22}, wherein:
R_{20} is —$(CH_2)_n$— where n is 2, 3, 4 or 5;
R_{21} is
—CH_2—CH=CH—CH_2—,
—CH_2—C≡C—CH_2—,
—CH_2—CH=CH—CH_2—CH_2—,
—CH_2—CH_2—CH=CH—CH_2—,
—CH_2—C≡C—CH_2—CH_2—, or
—CH_2—CH_2—C≡C—CH_2—,
the —CH=CH— bond being cis or trans;
R_{22} is R_{20} or R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one C_1–C_6 linear alkyl group, phenyl group or

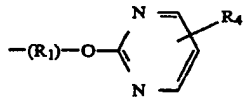


where Z_1 is lower alkyl, —OH, lower alkoxy, —CF_3, —NO_2, —NH_2 or halogen; and R and m are as defined hereinafter;



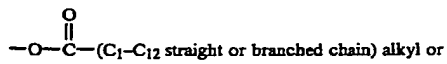
(2)

where R_1 is as previously defined, and R_3 is hydrogen or —OCH_3;

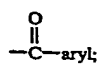


(3)

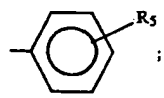
where R_1 is as previously defined; and
R_4 is hydrogen, lower alkyl, lower alkoxy, hydroxy, amino, mono- or dialkylamino, C_1–C_3 acyl amino, C_1–C_6 alkanoyl, trifluoromethyl, chlorine, fluorine, bromine,



(C1–C12 straight or branched chain) alkyl or

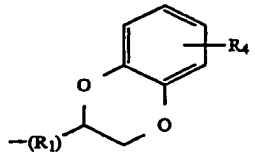


in which aryl is phenyl or



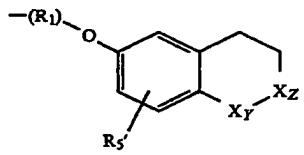
where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;

(4)



where R_1 and R_4 are as previously defined;

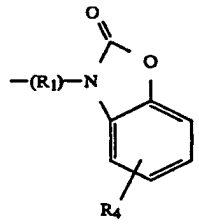
(5)



where either one of X_y or X_z is

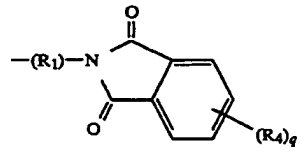
and the other is —CH_2—; and
R_5' is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, or bromine; and
R_1 is as previously defined;

(6)



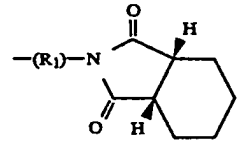
where R_1 and R_4 are as previously defined;

(7)



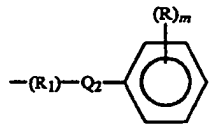
where q is 1, 2, 3 or 4, and R_1 and R_4 are as previously defined;

(8)



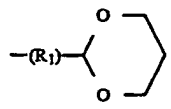
where R_1 is as previously defined;

(9)



where R_1 is as previously defined;
Q_2 is S, NH, or —CH_2—; and
R and m are as defined hereinafter;

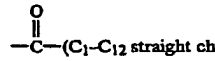
(10)



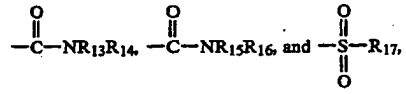
where R_1 is as previously defined;

—R_1—O—R_{12} (11)

where R_{12} is selected from the group consisting of:
hydrogen,



—C—(C_1–C_{12} straight chain or branched) alkyl,

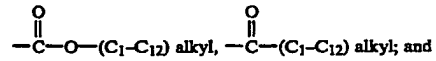


—C—$NR_{13}R_{14}$, —C—$NR_{15}R_{16}$, and —S—R_{17},

where R_{13} is selected from the group consisting of hydrogen and (C_1–C_{12}) alkyl groups;
where R_{14} is selected from the group consisting of hydrogen and (C_1–C_{12}) alkyl groups;
where $NR_{15}R_{16}$ taken together form a ring structure selected from the group consisting of piperidinyl, morpholinyl and piperazinyl;
where R_{17} is selected from the group consisting of lower alkyl and aryl groups;

—R_1—$NR_{18}R_{19}$ (12)

where R_{18} and R 19 are independently selected from the group consisting of:
hydrogen,
(C_1–C_{12} straight or branched chain) alkyl,

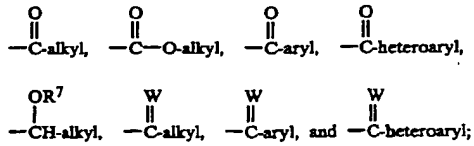


—C—O—(C_1–C_{12}) alkyl, —C—(C_1–C_{12}) alkyl; and

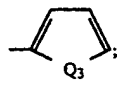
where $NR_{18}R_{19}$ taken together form a ring structure selected from the group consisting of piperidinyl, morpholinyl and piperazinyl;

—R_1—S—R_{12} (12)

where R_1 and R12 are as previously defined;
R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, formyl,

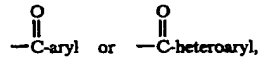


alkyl is lower alkyl;
aryl is as previously defined;
heteroaryl is



Q_3 is —O—, —S—,

—CH=N—;
W is CH_2 or CHR_8 or N—R_9;
R_7 is hydrogen, lower alkyl, or acyl;
R_8 is lower alkyl;
R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and
R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,

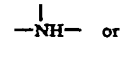


where aryl and heteroaryl are as defined above; and
m is 1, 2, or 3;
with the proviso that in formula (9) Z is not

when X is —S—, Q_2 is —CH_2—, Y is hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy or trifluoromethyl, and p is 1 or 2;
with the proviso that in formula (4) R_4 is not H when R_1 is R_{20}, Z is not

X is —S—, Y is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or trifluoromethyl, and p is 1 or 2;
with the proviso that in formula (9) Z is not

when X is



Y is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or trifluoromethyl and Q_2 is —CH_2—;
with the proviso that in formula (9) Z is not

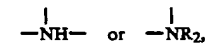
when X is —O—, Q_2 is —CH_2—, Y is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen, and p is 1 or 2;
with the proviso that in formula (9) Z is not

when X is —S—, Q_2 is —CH_2—, Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2, R is hydrogen, and m is 1;
with the proviso that in formula (9) Z is not

when X is

Q_2 is —CH_2—, R is chlorine, fluorine, bromine, iodine, lower alkyl, lower alkoxy, lower alkyl thio, lower mono- or dialkylamino, amino, cyano, hydroxy, trifluoromethyl; R_2 is aryl; Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2;
with the proviso that in formula (9) Z is not

when X is



where R_2 is lower alkyl, aryl lower alkyl, or phenylsulfonyl, Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2 and Q_2 is —CH_2—;
with the proviso that Y_2 is not the moiety of formula (8) when Z is

X is O, p is 1, and Y is hydrogen, Lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;
with the proviso that in formula (1) Z is not

when X is O or S, Y is hydrogen, R is hydrogen, C_1–C_4 alkyl, chlorine, fluorine, bromine, iodine, cyano, C_1–C_4 alkoxy, aryl, —$COOR_{23}$ where R_{23} is C_1–C_4 alkyl;
with the proviso that in formula (1) Z is not

—N—

when X is —S—, R_1 is R_{20}, R is H, and m=1;
with the proviso that in formula (7) R_4 is not hydrogen when Y is 6-F, X is —O—, Z is

—CH—,

and n is 2, 3 or 4;
with the proviso that in formula (11) R_{12} is not H when Z is

—N—,

X is

—NH— or —NR_2

where R_2 is lower alkyl, aryl lower alkyl, or phenylsulfonyl Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group and p is 1 or 2;
with the proviso that in formula (11) , R_{12} is not H when X is

—NR_2,

where R_2 is phenyl, Z is

—N—,

and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;
with the proviso that in formula (12), R_{18} and R_{19} are not lower alkyl when Z is

—N—,

X is

—NR_2

and R_2 is aryl and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;
with the proviso that in formula (12), when X is —O—, Z is

—CH—,

and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group, R_{18} and R_{19} are not lower alkyl;
with the proviso that in formula (12), R_{18} and R_{19} are not hydrogen when R_1 is R_{20}, Z is

—CH—,

X is —O—, and Y is 6-F;
all geometric optical and stereoisomers thereof, or a pharmaceutically acceptable acid addition salt thereof

This invention also provides a pharmaceutical composition, which comprises a compound of the invention and a pharmaceutically acceptable carrier therefor. In one embodiment of the invention, the pharmaceutical composition is an antipsychotic composition comprising a compound of the invention in an amount sufficient to produce an antipsychotic effect.

In addition, this invention provides a method of treating psychoses, which comprises administering to a patient a pharmaceutically effective amount of a compound of the invention.

Finally, this invention provides a method of alleviating pain by administering to a patient a pain-relieving amount of a compound of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The compounds of this invention are useful as antipsychotic drugs and as analgesic agents. The compounds of the invention can contain a variety of different substituents and chemical groups. As used herein, when the term "lower" is mentioned in connection with the description of a particular group, the term means that the group it is describing contains from 1 to 6 carbon atoms.

The term "alkyl" as used herein refers to a straight or branched chain hydrocarbon group containing no unsaturation, for example, methyl, ethyl, isopropyl, 2-butyl, neopentyl, or n-hexyl.

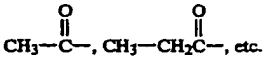
The term "alkoxy" as used herein refers to a monovalent substituent comprising an alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen, e.g. methoxy, ethoxy, propoxy, butoxy, or pentoxy.

The term "alkylene" as used herein refers to a bivalent radical of a lower branched or unbranched alkyl group having valence bonds on two terminal carbons thereof, for example, ethylene (—CH_2CH_2—), propylene (—$CH_2CH_2CH_2$—), or isopropylene

(—CH_2CHCH_2—).

The term "cycloalkyl" refers to a saturated hydrocarbon group possessing at least one carbocyclic ring, the ring containing from 3 to 10 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclodecyl and the like.

The term "alkanoyl" refers to the radical formed by removal of the hydroxyl function from an alkanoic acid. More particularly, the term "alkanoyl" as used herein refers to an alkyl carbonyl moiety containing from 2 to 11 carbon atoms, e.g.



Examples of alkanoyl groups are formyl, acetyl, propionyl, 2,2-dimethylacetyl, hexanoyl, octanoyl, decanoyl, and the like.

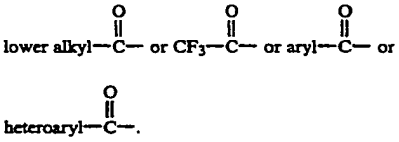
The term "alkanoic acid" refers to a compound formed by combination of a carboxyl group with a hydrogen atom or alkyl group. Examples of alkanoic acids are formic acid, acetic acid, propanoic acid, 2,2-dimethylacetic acid, hexanoic acid, octanoic acid, decanoic acid, and the like.

The term "aryl lower alkyl" refers to compounds wherein "aryl" and "loweralkyl" are as defined above.

The term "lower alkylthio" refers to a monovalent substituent having the formula lower alkyl—S—.

The term "phenylsulfonyl" refers to a monovalent substituent having the formula phenyl-SO_2—.

The term "acyl" refers to a substituent having the formula



The term "lower monoalkylamino" refers to a monosubstituted derivative of ammonia, wherein a hydrogen of ammonia is replaced by a lower alkyl group.

The term "lower dialkylamino" refers to a disubstituted derivative of ammonia, wherein two hydrogens of ammonia are replaced by lower alkyl groups.

The term "acylamino" refers to a primary or secondary amine, wherein a hydrogen of the amine is replaced by an acyl group, where acyl is as previously defined.

The term "dialkylaminocarbonyl" refers to a derivative of an acid, wherein the hydroxyl group of the acid is replaced by a lower dialkylamino group.

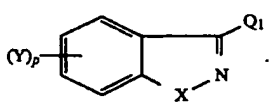
The term "aroyl" refers to a disubstituted carbonyl, wherein at least one substituent is an aryl group, where "aryl" is as previously defined.

Unless otherwise indicated, the term "halogen" as used herein refers to a member of the halogen family selected from the group consisting of fluorine, chlorine, bromine, and iodine.

Throughout the specification and appended claims, a given chemical formula or name shall encompass all geometric, optical and stereoisomers thereof where such isomers exist.

A. COMPOUNDS OF THE INVENTION

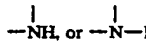
The compounds of this invention can be represented by the following formula:



(I)

wherein

X is —O—, —S—,



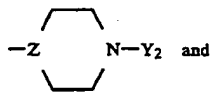
R_2 is selected from the group consisting of lower alkyl, aryl lower alkyl, aryl, cycloalkyl, aroyl, alkanoyl, and phenylsulfonyl groups;

p is 1 or 2;

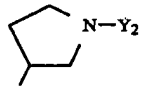
Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—;

Q_1 is selected from the group consisting of:

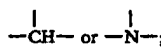


(a)



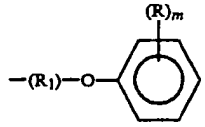
(b)

where Z is



and

Y_2 is selected from the group consisting of:



(1)

in which (R_1) is R_{20}, R_{21} or R_{22}, wherein

R_{20} is $—(CH_2)_n—$ where n is 2, 3, 4 or 5;

R_{21} is

$—CH_2—CH=CH—CH_2—$,

$—CH_2—C\equiv C—CH_2—$,

$—CH_2—CH=CH—CH_2—CH_2—$,

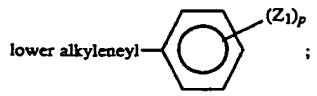
$—CH_2—CH_2—CH=CH—CH_2—$,

$—CH_2—C\equiv C—CH_2—CH_2—$, or

$—CH_2—CH_2—C\equiv C—CH_2—$,

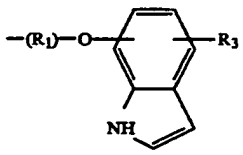
the —CH=CH— bond being cis or trans;

R_{22} is R_{20} or R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one C_1-C_6 linear alkyl group, phenyl group or



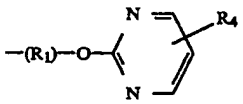
;

where Z_1 is lower alkyl, —OH, lower alkoxy, —CF_3, —NO_2, —NH_2 or halogen; and R and m are as defined hereinafter;



(2)

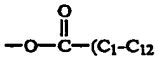
where R_1 is as previously defined, and R_3 is hydrogen or $-OCH_3$;



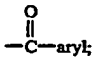
(3)

where R_1 is as previously defined; and

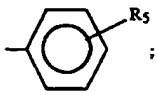
R_4 is hydrogen, lower alkyl, lower alkoxy, hydroxy, amino, mono- or dialkylamino, C_1–C_3 acyl amino, C_1–C_6 alkanoyl, trifluoromethyl, chlorine, fluorine, bromine,



straight or branched chain) alkyl or

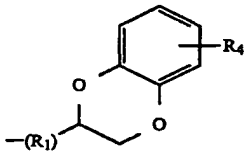


in which aryl is phenyl or



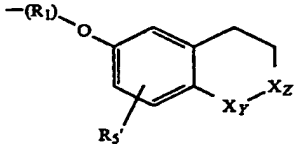
;

where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;



(4)

where R_1 and R_4 are as previously defined;



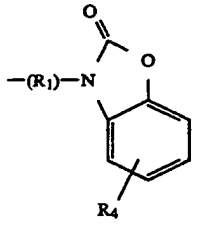
(5)

where either one of X_y or X_z is

and the other is $-CH_2-$; and

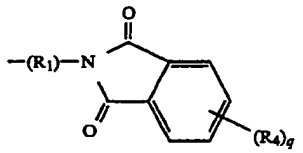
R_5' is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, or bromine; and

R_1 is as previously defined;



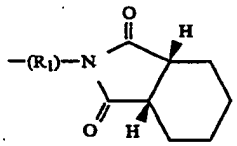
(6)

where R_1 and R_4 are as previously defined;



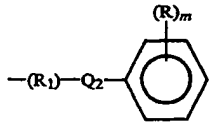
(7)

where q is 1, 2, 3 or 4, and R_1 and R_4 are as previously defined;



(8)

where R_1 is as previously defined;

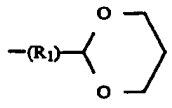


(9)

where R_1 is as previously defined;

Q_2 is S, NH, or $-CH_2-$; and

R and m are as defined hereinafter;

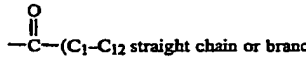


(10)

where R_1 is as previously defined;

(12)

where R_{12} is selected from the group consisting of: hydrogen,



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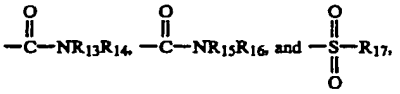
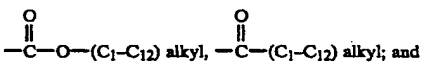


where R_{13} is selected from the group consisting of hydrogen and (C_1–C_{12}) alkyl groups;
where R_{14} is selected from the group consisting of hydrogen and (C_1–C_{12}) alkyl groups;
where $NR_{15}R_{16}$ taken together form a ring structure selected from the group consisting of piperidinyl, morpholinyl and piperazinyl;
where R_{17} is selected from the group consisting of lower alkyl and aryl groups;

$$-R_1-NR_{18}R_{19} \quad (12)$$

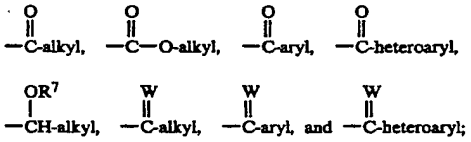
where R_{18} and R_{19} are independently selected from the group consisting of:
hydrogen;



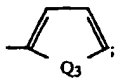
where $NR_{18}R_{19}$ taken together form a ring structure selected from the group consisting of piperidinyl, morpholinyl and piperazinyl;

$$-R_1-S-R_{12} \quad (13)$$

where R_1 and R_{12} are as previously defined;
R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, formyl,

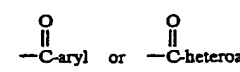


alkyl is lower alkyl;
aryl is as previously defined;
heteroaryl is



Q_3 is —O—, —S—,

—CH=N—;
W is CH_2 or CHR_8 or N—R_9;
R_7 is hydrogen, lower alkyl, or acyl;
R_8 is lower alkyl;
R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and
R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,



where aryl and heteroaryl are as defined above; and
m is 1, 2, or 3;
with the proviso that in formula (9) Z is not

when X is —S—, Q_2 is —CH_2—, Y is hydrogen, lower alkyl, lower alkoxy, halogen, hydroxy or trifluoromethyl, and p is 1 or 2;
with the proviso that in formula (4) R_4 is not H when R_1 is R_{20}, Z is not

X is —S—S, Y is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or trifluoromethyl, and p is 1 or 2;
with the proviso that in formula (9) Z is not

when X is

Y is hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or trifluoromethyl and Q_2 is —CH_2—;
with the proviso that in formula (9) Z is not

when X is —O—, Q_2 is —CH_2—, Y is hydrogen, lower alkyl, lower alkoxy, hydroxy or halogen, and p is 1 or 2;
with the proviso that in formula (9) Z is not

when X is —S—, Q_2 is —CH_2—, Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2, R is hydrogen, and m is 1;
with the proviso that in formula (9) Z is not

when X is

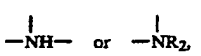
Q_2 is —CH_2—, R is chlorine, fluorine, bromine, iodine, lower alkyl, lower alkoxy, lower alkyl thio, lower mono- or dialkylamino, amino, cyano, hydroxy, trifluo-

romethyl; R_2 is aryl; Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2;

with the proviso that in formula (9) Z is not

when

X is



where R_2 is lower alkyl, aryl lower alkyl, or phenylsulfonyl, Y is hydrogen, halogen, lower alkyl, lower alkoxy or hydroxy, p is 1 or 2 and Q_2 is $—CH_2—$;

with the proviso that Y_2 is not the moiety of formula (8) when Z is

X is O, p is 1, and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

with the proviso that in formula (1) Z is not

when X is O or S, Y is hydrogen, R is hydrogen, C_1–C_4 alkyl, chlorine, fluorine, bromine, iodine, cyano, C_1–C_4 alkoxy, aryl, $—COOR_{23}$ where R_{23} is C_1–C_4 alkyl;

with the proviso that in formula (1) Z is not

when X is —S—, R_1 is R_{20}, R is H, and m = 1;

with the proviso that in formula (7) R_4 is not hydrogen when Y is 6 -F, X is —O—, Z is

and n is 2, 3 or 4;

with the proviso that in formula (11) R_{12} is not H when Z is

X is

where R_2 is lower alkyl, aryl lower alkyl, or phenylsulfonyl Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group and p is I or 2;

with the proviso that in formula (11), R_{12} is not H when X is

where R_2 is phenyl, Z is

and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

with the proviso that in formula (12), R_{18} and R_{19} are not lower alkyl when Z is

X is

R_2 is aryl and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group;

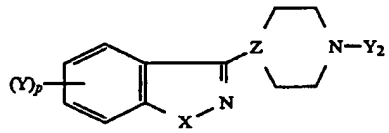
with the proviso that in formula (12), when X is —O—, Z is

and Y is hydrogen, lower alkyl, lower alkoxy, chlorine, fluorine, bromine, iodine or a hydroxyl group, R_{18} and R_{19} are not lower alkyl;

with the proviso that in formula (12), R_{18} and R_{19} are not hydrogen when R_1 is R_{20}, Z is —CH—, X is —O—, and Y is 6-F;

all geometric optical and stereoisomers thereof, or a pharmaceutically acceptable acid addition salt thereof.

The compounds of the invention can also be represented by the following formula:



The substituent X in formula (I) is selected from the group consisting of —O—, —S—, —NH—, or

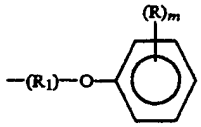
When the substituent X is —O—, the compounds of the invention contain a 1,2-benzisoxazole nucleus, and when X is —S—, the compounds of the invention contain a 1,2-benzisothiazole nucleus. When X is —NH— or

the compounds of the invention contain the indazole nucleus.

When p in formula (I) is 1, the substituent Y is selected from the group consisting of hydrogen, lower alkyl, hydroxyl, halogen, lower alkoxy, $—CF_3$, $—NO_2$, and $—NH_2$. The substituent Y is preferably in the 5- or 6-position of the ring. Moreover, in the preferred embodiments of the invention, the substituent Y is hydrogen, chlorine, bromine, or fluorine, and in the particularly preferred compounds of the invention, Y is fluorine, especially in the 6-position of the ring.

When p in formula (I) is 2 and X is —O—, each Y substituent can be independently selected from lower alkoxy, hydroxy or halogen groups, preferably methoxy groups.

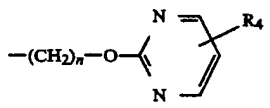
When the substituent Y2 has the formula (b)(1):



and R_1 contains unsaturation, R_1 preferably has the formula

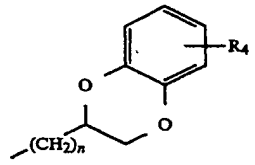
$$—CH_2—CH=CH—CH_2—.$$

When the substituent Y_2 has the formula (b)(3):

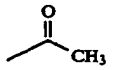


the substituent R_4 is preferably hydrogen or C_1–C_6 alkyl carbonyl and n is 3.

When the substituent Y_2 has the formula (b) (4):

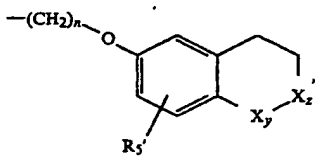


the substituent R_4 is preferably hydrogen or



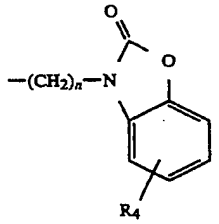
and n is preferably 1 or 2.

When the ,substituent Y_2 has the formula (b)(5):

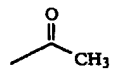


the substituent R_5' is preferably $—OCH_3$ and n is preferably 3.

When the substituent R_4 has the formula (b)(6):

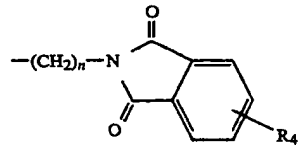


the substituent R_4 is preferably



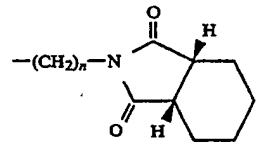
and n is preferably 3.

When the substituent Y_2 has the formula (b) (7):



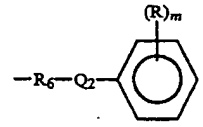
the substituent R_4 is preferably hydrogen and n is preferably 3 or 4.

When the substituent Y_2 has the formula (b) (8):



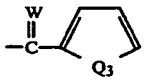
the value of n is preferably 3 or 4.

When the substituent Y_2 has the formula (b) (9):



the substituent R_6 is preferably $—CH_2—CH=C-H_2—CH_2—$ when R_6 contains unsaturation.

When the substituent R is



the substituent Q_3 is preferably —CH=N; and the substituent W is preferably CH_2, the substituent R_8 in CHR_8 is preferably CH_3, the substituent R_9 in N—R_9 is preferably hydroxy, lower alkoxy, or NH_2, and the substituent R_{10} in NHR_{10} is preferably hydrogen.

The value of n in the foregoing formulas can be 2, 3, 4, or 5, and preferably is 2, 3, or 4. In the particularly preferred compounds of the invention n is 3.

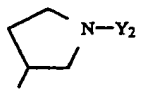
When X in the compounds of the invention is

the substituent R_2 is selected from the group consisting of lower alkyl, aryl lower alkyl, aryl, cycloalkyl, aroyl, alkanoyl, and phenylsulfonyl groups.

The substituent Z can be

in which case the compounds of the invention are heteroarylpiperidine derivatives, or

in which case the compounds are heteroarylpiperazine derivatives. When the substituent Q_1 has the formula

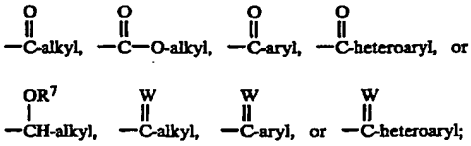


the compounds of the invention are heteroarylpyrrolidines. The preferred compounds of the invention are the heteroarylpiperidines, i.e. compounds in which Z is

The compounds of the invention can contain one, two, or three R-substituents. The substituent R can be hydrogen, lower alkyl, C_1–C_6 alkoxy, hydroxyl, carboxyl, Cl, F, Br, I, amino, C_1–C_6 mono or dialkyl amino, —NO_2, lower alkyl thio, —OCF_3, cyano, acylamino, —CF_3, trifluoroacetyl (i.e.

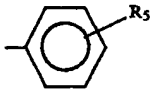
aminocarbonyl (i.e.

dialkylaminocarbonyl, formyl,



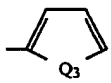
alkyl is lower alkyl;

aryl is phenyl or



(1)

where R_5 is hydrogen, lower alkyl, C_1–C_6 alkoxy, hydroxy, Cl, F, Br, I, C_1–C_6 alkylamino, —NO_2, —CN, —CF_3, —OCF_3; heteroaryl is



(2)

Q is —O—, —S—,

—CH=N—;

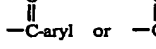
W is CH_2 or CHR_8 or N—R_9;

R_7 is hydrogen, lower alkyl, or acyl;

R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or —NHR10; and

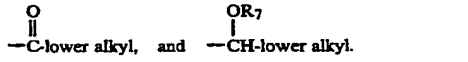
R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,



heteroaryl, where aryl and heteroaryl are as defined above; and

m is 1, 2, or 3.

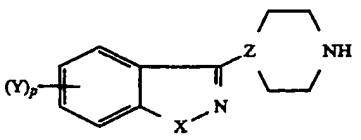
When the compounds of the invention contain two or three R-substituents, each of the R-substituents can be independently selected from the above substituents. Preferably, each of the R-substituents is selected from the group consisting of hydrogen, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl, —$COCF_3$, C_1–C_6 alkanoyl, Cl, F, Br, I, C_1–C_3 alkylamino, —NO_2, —CF_3, —OCF_3,



The compounds of the present invention are prepared in the following manner. The substituents R, R_1, R_2, R_3, X, Y, and Z and the integers m, n, and p are as defined above unless indicated otherwise.

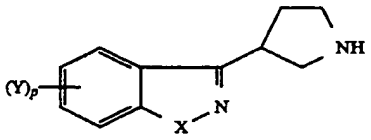
B. PREPARATION OF COMPOUNDS OF THE INVENTION

The compounds of the invention can be prepared by reacting a piperidine or a piperazine of the formula:



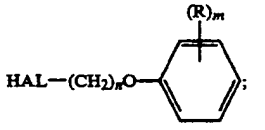
(3)

or a pyrrolidine of the formula:



(3A)

under alkylating conditions with a compound of the formula:

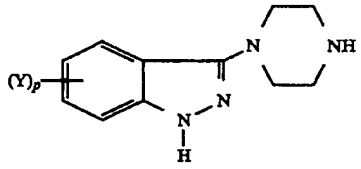


(4)

where HAL is Cl, Br, or I. The procedures that can be employed for preparing the piperidines, the piperazines, and the pyrrolidines and the alkylating agents identified by the above formulas will now be described in detail.

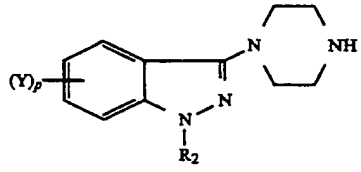
1. Preparation of 3-(1-unsubstituted-4-piperazinyl)-1H-indazoles

Compounds of the formulae:



(5)

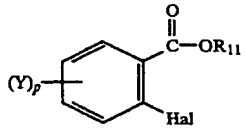
and



(6)

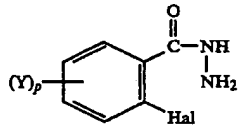
for use in synthesizing the indazoyl-substituted piperazines of the invention can be prepared as follows.

A substituted aryl ester of formula (7) is selected,



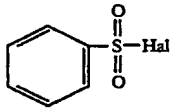
(7)

where R_{11} is lower alkyl and Hal is a halogen selected from the group consisting of Cl, Br, and I. The ester of formula (7) is reacted with hydrazine, H_2NNH_2, under standard hydrazide formation conditions. Typically, the reaction is carried out in a nonreactive solvent, e.g. ethanol, methanoL, or toluene, at a temperature of ambient temperature to the reflux temperature of the solvent for 4 to 16 hours to form a hydrazide of formula (8):



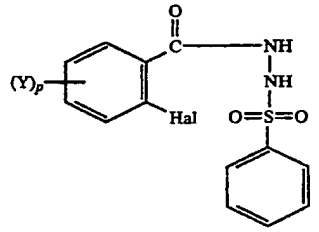
(8)

The hydrazide of formula (8) is reacted with a phenyl sulfonyl halide of the formula



(9)

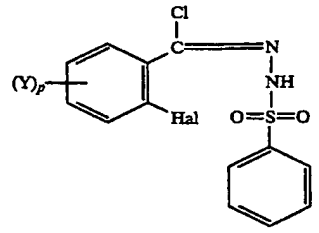
where Hal is a halogen selected from the group consisting Cl and Br, to form a compound of the formula



(10)

Typically this reaction is carried out in a basic solvent, such as pyridine or collidine, at a temperature of 0° to 30° C. for 2 to 16 hours.

The compound of formula (10) in turn is reacted neat with thionyl chloride at a temperature of 50° to 79° C. (reflux temperature) for 2 to 16 hours to form a compound of formula (11)

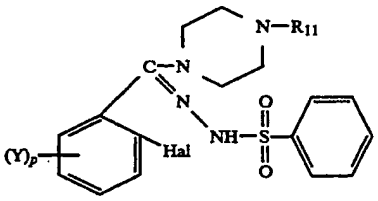


(11)

Compound (11) is reacted with a compound of formula (12) ,

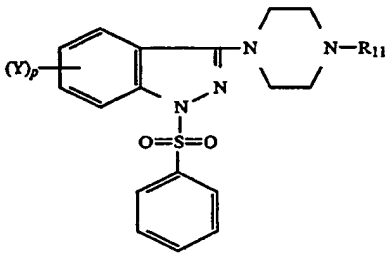
(12)

where R_{11} is lower alkyl, under conventional nucleophilic reaction conditions, for example in an inert solvent, such as tetrahydrofuran (THF), toluene, or diethylether, at a temperature of 5° to 50° C. for 1 to 16 hours to form a compound having the formula



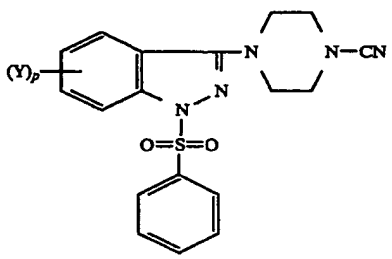
(13)

The compound of formula (13) is then reacted with a condensation agent, such as copper, copper-bronze, or cuprous oxide, in a solvent such as dimethylformamide, dimethylacetamide, or tetramethylurea, at a temperature of 120° to 177° C. for 1 to 16 hours to form a piperazine-substituted phenylsulfonyl indazole of the formula



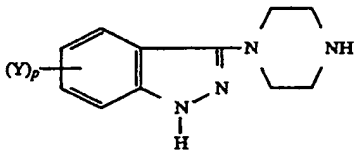
(14)

A cyano-substituted piperazine phenylsulfonyl indazole is then formed by reacting the compound of formula (14) with a conventional cyanation source, such as a halo-cyanide, e.g. BrCN or ClCN, under conventional cyanation conditions, typically in an inert solvent, e.g. dimethylsulfoxide (DMSO) or $CHCl_3$, at ambient temperature for 2 to 16 hours to form a compound of formula



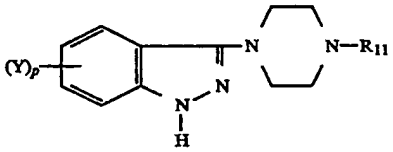
(15)

The compound of formula (15) is then subjected to reduction by means of a metal hydride, e.g. lithium aluminum hydride ($LiAlH_4$). Typically the reduction is carried out under standard reduction conditions in a solvent, such as tetrahydrofuran or diethyl ether, at a temperature of 35° to 67° C. for 6 to 16 hours to forth a compound of formula (16):



(16)

A compound of formula (16) can be formed in an alternative manner by first reacting a compound of formula (14) with a strong base, such as a metal alcoholate, e.g. sodium methoxide, sodium ethoxide, or sodium butoxide, or with KOH in tetrahydrofuran to form a compound of formula (17):

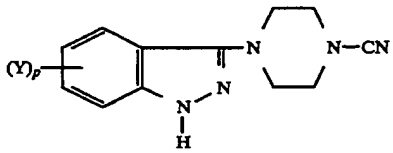


(17)

This reaction is typically carried out in a polar solvent, such as for example CH_3OH or C_2H_5OH, at a temperature of ambient to 50° C. for 1 to 16 hours.

Alternatively, the compound of formula (17) can be formed by reducing compound (14) with $LiAlH_4$ under conditions as previously described.

The compound of formula (17) in turn can be reacted with a cyanation reagent, as previously described, to form a cyano substituted piperazine indazole of the formula



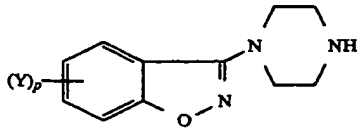
(18)

which in turn can be reduced with a metal hydride, as previously described, to form a compound of formula (16).

In an alternative embodiment, a compound of formula (18) can be reacted with an aqueous mineral acid, e.g. H_2SO_4 or HCl, at a temperature of 50° to 120° C. for 2 to 16 hours to form a compound of formula (16).

2. Preparation of 3-(1-unsubstituted-4-piperazinyl)-1,2-benzisoxazoles

A compound of the formula:

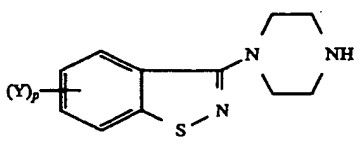


(19)

can be prepared according to conventional techniques. Suitable procedures are described in J. Med. Chem. 1986, 29:359. Compounds of formula (19) are useful for synthesizing the benzisoxazole substituted piperazines of the invention.

3. Preparation of 3-(1-unsubstituted-4-piperazinyl)-1,2-benzisothiazoles

A compound of the formula:

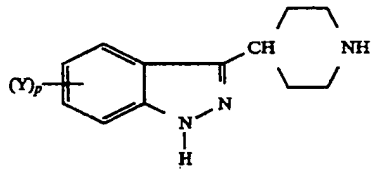


(20)

for use in synthesizing the benzisothiazole substituted piperazines of the invention can be prepared according to the techniques described in J. Med. Chem. 1986, 29:359 and United Kingdom Patent (GB) 2 163 432 A.

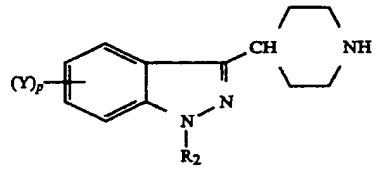
4. Preparation of 3-(1-unsubstituted-4-piperidinyl)-1H-indazoles

A compound of the formula:



(21)

or

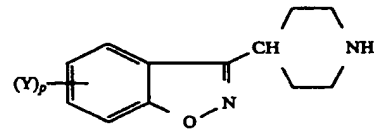


(22)

for use in synthesizing the indazole-substituted piperidines of the invention can be prepared using known techniques. For example, suitable techniques are described in substantial detail in U.S. Pat. 4,710,573.

5. Preparation of 3-(1-unsubstituted-4-piperidinyl)-1,2-benzisoxazoles

A compound of the formula:

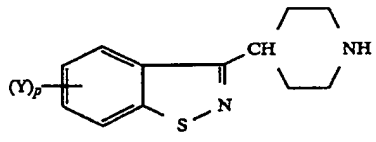


(23)

can be prepared by following the teachings from several sources. For example, U.S. Pat. No. 4,355,037 contains a detailed description of compounds of formula (23) and of methods for preparing the compounds. Additional disclosure of methods for preparing the compounds of formula (23) can be found in U.S. Pat. No. 4,327,103 and in Strupczewski et al., J. Med. Chem., 28:761–769 (1985). The compounds of formula (23) can be employed in the synthesis of the benzisoxazole substituted piperidines of the invention.

6. Preparation of 3-(1-unsubstituted-4-piperidinyl)-1,2-benzisothiazoles

Certain 3-(4-piperidinyl)-1,2-benzisothiazoles can be employed in the synthesis of the N-(aryloxyalkyl)-heteroaryl piperidines of the invention. Specifically, a benzisothiazole of the formula:

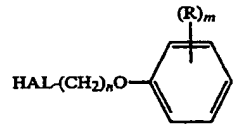


(24)

can be reacted with the alkylating agent previously described to form the N-(aryloxyalkyl)heteroarylpiperidines of the invention. Compounds of formula (24) and their methods of preparation are described in detail in U.S. Pat. No. 4,458,076.

7. Preparation of alkylating agents

The compounds described in Sections 1–6 above can be reacted with alkylating agents of the formula:



(4)

to form the N-(aryloxyalkyl)heteroarylpiperidines, piperazines, and pyrrolidines of the invention. The alkylating agents of formula (4) and methods for preparing the alkylating agents are described in U.S. Pat. No. 4,366,162. Additional disclosure can be found in South African publication EA 86 14522. In addition, procedures for making alkylating agents are described in the following Examples. These procedures can be employed to make other alkylating agents for use in this invention.

8. Alkylation of heteroarylpiperidines, piperazines, and pyrrolidines to form the compounds of the invention

The heteroarylpiperidines, piperazines, and pyrrolidines described in Sections 1–6 above can be reacted under alkylating conditions with the alkylating agents described in Section 7 to form the compounds of this invention. The reaction can be carried out by dissolving the reagents in an inert solvent, such as dimethylformamide, acetonitrile, or butanol, and allowing the reagents to react from a temperature of 50° C. to refluxing of the solvent in the presence of an acid receptor, such as a base. Examples of suitable bases are alkali metal carbonates, such as potassium carbonate, sodium carbonate, or sodium bicarbonate. The reaction can be carried out with or without a catalytic amount of an alkaline iodide, such as potassium iodide or sodium iodide, for a time sufficient to form a compound of formula (I) of the invention. Generally, the alkylation reaction is carried out for about 4 to about 16 hours, depending on reactivity of the reagents. The reaction temperature can vary from about 50° to about 120° C. The products can be isolated by treating the reaction product with water, extracting the product into an or-

ganic solvent that is immiscible in water, washing, drying, and concentrating the organic solvent to yield the free base, and then, if indicated, converting the resulting compound to an acid addition salt in a conventional manner.

Following are typical examples of compounds of the invention that can be prepared by following the techniques described above:

1-[4-[3-[4-(1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone;
1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3methoxyphenyl]ethanone;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone;
1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3methoxyphenyl]ethanone;
1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone;
1-[4-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone fumarate;
1-[4-[4-[4-(1H-indazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone fumarate;
[4-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone;
[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxy-α-methylbenzenemethanol;
[4-[3-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone;
[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxyphenyl]ethanone;
[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]-propoxy]-3-methoxyphenyl]ethanone;
[4-[4-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone;
1-[4-[3-[4-(1H-indazol-3-yl)-1-piperidinyl]propoxy]-3methoxyphenyl]ethanone;
1-[4-[3-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone;
1-[4-[4-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone fumarate;
[4-[3-[4-(5-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone;
6fluoro-3-[1-[3-(2-methoxyphenoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate;
[4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]phenylmethanone;
1-[4-[4-[4-(1H-indazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone;
1-[4-[2-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone;
1-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone fumarate;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-methylphenyl]ethanone;
1-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-5-methylphenyl]ethanone;
N-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]acetamide hemifumarate;
6-chloro-3-(1-piperazinyl)-1H-indazole;
1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methylphenyl]ethanone hemifumarate;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone;
1-[4-[3-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]-propoxy]-3-methoxyphenyl]ethanone;
1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone;
4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzonitrile;
1-[4-[4-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl]-butoxy]-3-methoxyphenyl]ethanone;
1-[4-[3-[4-(1-benzoyl-6-fluoro-1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone sesquifumarate;
1-[4-[4-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]-butoxy]-3-methoxyphenyl]ethanone;
1-[4-[3-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-propoxy]-3-methoxyphenyl]ethanone hemifumarate;
1-[3,5-dibromo-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone;
1-[4-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethoxy]-3-methoxyphenyl]ethanone;
6-fluoro-3-[1-(3-phenoxypropyl)-4-piperidinyl]-1,2-benzisoxazole;
1-[4-[2-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]-ethoxy]-3-methoxyphenyl]ethanone;
1-[4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methylmercaptophenyl]ethanone;
1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]phenylmethanone;
1-[3-bromo-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone;
3-[1-[3-[4-(1-ethoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole hydrochloride;
3-[1-[3-[4-(1-acetoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole fumarate;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy-3-methoxyphenyl]pentanone;
2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperdinyl]-propoxy]-N-methylbenzenamine hemifumarate;
3-[1-[3-(4-bromo-2-methoxphenoxy)propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]propanone;
4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzamide;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-(methylamino)phenyl]ethanone;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-ethoxyphenyl]ethanone;
N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-dimethylaminophenyl]ethanone;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-methoxyphenyl]ethanone hydrochloride;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]-2,2,2-trifluoroethanone;
4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxy-α-methylbenzenemethanol;

2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline dihydrochloride;
N-[5-acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide;
3-[1-[3-(4-ethyl-3-methoxyphenoxy)propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole hydrochloride;
1-[3,5-dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone;
N-[3-[3-[4-(6-fluoro-1,2-benxoisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide hemifumarate;
3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline;
3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyaniline;
1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy-3-methylaminophenyl]ethanone fumarate;
N-[3-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]acetamide;
1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrochloride;
N,N-dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone oxime;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-methoxyphenyl]ethanone oxime O-methyl ether;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrazone;
6-fluoro-3-[1-[3-[2-methoxy-4-(1-methylethenyl)-phenoxy]propyl]-4-piperidinyl]-1,2-benzisoxazole hydrochloride;
(Z)-1-[4-[(4-chloro-2-butenyl)oxy]-3-methoxyphenyl]ethanone;
(Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl]ethanone;
(E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-hydroxyphenyl]ethanone hydrochloride;
(E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-benzyloxyphenyl]ethanone;
6-(3-chloropropoxy)-5-methoxy indole;
6-fluoro-3-[1-[3-[(5-methoxy-1H-indol-6-yl)oxy]-propyl]-4-piperidinyl]-1,2-benzisoxazole;
6-fluoro-3-[1-[3-[(1H-indol-7-yl)oxy]propyl]-4-piperidinyl]01,2-benzisoxazole hemifumarate;
6-fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole;
6-fluoro-3-[1-(2-pyrimidinoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate;
6-aceto-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan;
2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-methyl-1,4-benzodioxan;
2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl-1,4-benzodioxan;
6-(3-chloropropoxy)-7-methoxy-1-tetralone;
6-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-7-methoxy-1-tetralone;
N-(3-chloropropyl)-2-benzoxazolinone;
N-(3-chloropropyl)-6-acetyl-2-benzoxazolinone;
N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propyl]-6-acetyl-2-benzoxazolinone;
N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propyl]phthalimide;
1-(3-aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride;
cis-2-(3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)propyl-hexahydro-1H-isoindole-1,3-dione hydrochloride;
N-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-butyl]phthalimide;
1-(4-aminobutyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride;
cis-(2-(4-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl) butyl)-hexahydro-1H-isoindole-1,3-dione hydrochloride;
1-[4-[[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]thio]-3-methoxyphenyl]ethanone;
4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2'-methoxyphenyl) butylpiperidine maleate;
4-(4-bromobutyl)-1-(1,3-dithian-2-yl)ethylbenzene;
1-[4-(1,3-dithian-2-yl)ethyl]phenyl-4-(6-fluoro-1,2-benzisoxazol-3-yl)butylpiperidine;
1-[4-(4'-acetophenyl)butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3-methoxyphenyl]ethanone;
(2,4-difluorophenyl)-[1-(phenylmethyl)-3-pyrrolidinyl]-methanone oxalate;
6-fluoro-3-[1-phenylmethyl)-3-pyrrolidinyl]-1,2-benzisoxazole fumarate;
(E)-1-[4-[(4-bromo-2-butenyl)oxy]-3-methoxyphenyl]ethanone;
4-(3-chloropropoxy)-3-methoxybenzaldehyde;
6-fluoro-3-(3-pyrrolidinyl)-1,2-benzisoxazole hydrochloride;
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3-hydroxyphenyl]ethanone;
1-[3-acetylamino-4-(3-chloropropoxy)phenyl]ethanone;
N-[2-(3-hydroxypropoxy)phenyl]acetamide;
4-(3-chloropropoxy)-3-methoxybenzaldehyde;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methylpropoxy]-3-methoxyphenyl]ethanone;
(S)-(+)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methylpropoxy]-3-methoxyphenyl]ethanone;
(R)-(−)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methylpropoxy]-3-methoxyphenyl]ethanone;
1-[4-[3-[4-[(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2,2-dimethylpropoxy]-3-methoxyphenyl-]ethanone;
(±)-1-[1-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-phenylpropoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-(3-chlorophenyl)propoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-(phenylmethyl)propoxy]-3methoxyphenyl]ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-1-methylpropoxy]-3-methoxyphenyl]ethanone;

(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methylpropoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methylbutoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-phenylbutoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-(2-phenylethyl)butoxy]-3-methoxyphenyl]ethanone;
(±)-[4-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-1-methylethoxy]-3-methoxyphenyl]ethanone;
(E)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-1-methyl-2-butenyl]oxy]-3-methoxyphenyl]ethanone;
(Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methyl-2-butenyl]oxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-1-propyl-2-butynyl]oxy]-3-methoxyphenyl]ethanone;
(S)-(+)-1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]-2-methylpropoxy]-3-methoxyphenyl]ethanone;
(R)-(−)-1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]-2-methylpropoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-3-methylbutoxy]-3-methoxyphenyl]ethanone;
(±)-1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-phenylpropoxy]-3-methoxyphenyl]ethanone; and
(±)-6-fluoro-3-[1-[3-(2-methyl-(2-methoxyphenoxy)-propyl]-4-piperidinyl]-1,2-benzisoxazole.

The compounds of the present invention are useful for treating psychoses by virtue of their ability to elicit an antipsychotic response in mammals. Antipsychotic activity is determined in the climbing mice assay by a method similar to those described by P. Protais, et al., Psychopharmacol., 50:1 (1976) and B. Costall, Eur. J. Pharmacol., 50:39 (1978).

Subject CK-1 male mice (23–27 grams) are group-housed under standard laboratory conditions. The mice are individually placed in wire mesh stick cages (4″×10″) and are allowed one hour for adaption and exploration of the new environment. Then apomorphine is injected subcutaneously at 1.5 mg/kg, a dose causing climbing in all subjects for 30 minutes. Compounds to be tested for antipsychotic activity are injected intraperitoneally or given oral doses at various time intervals, e.g. 30 minutes, 60 minutes, etc. prior to the apomorphine challenge at 8 screening dose of 10–60 mg/kg.

For evaluation of climbing, 3 readings are taken at 10, 20, and 30 minutes after apomorphine administration according to the following scale:

Climbing Behavior Mice with:	Score
4 paws on bottom (no climbing)	0
2 paws on the wall (rearing)	1
4 paws on the wall (full climb)	2

Mice consistently climbing before the injection of apomorphine are discarded.

With full-developed apomorphine climbing, the animals are hanging on to the cage walls, rather motionless, over long periods of time. By contrast, climbs due to mere motor stimulation usually only last a few seconds.

The climbing scores are individually totaled (maximal score: 6 per mouse over 3 readings) and the total score of the control group (vehicle intraperitoneally-apomorphine subcutaneously) is set to 100%. ED_{50} values with 95% confidence limits, calculated by a linear regression analysis, of some of the compounds of the present invention as well as a standard antipsychotic agent are presented in Table 1.

TABLE 1

COMPOUND	CLIMBING MOUSE ASSAY (ED_{50} mg/kg, ip)
1-[4-[3-[4-(1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone	0.98
1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone	0.67
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone	0.095
1-[4-[4-[4-(1,2-benzisoxazol-3-yl-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone	1.6
1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone	0.68
1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrochloride	0.16
2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,4-benzodioxan	0.29
(Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl]ethanone	0.61
1-[4-(4′-acetophenyl)butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine	0.34
6-fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole	4.1
4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl decanoate fumarate	3.31
1-(3-aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride	22.6
N-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]phthalimide	5.0
6-fluoro-3-[1-[3-[(isoquinol-5-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole sesquifumarate	0.172
Chlorpromazine (standard)	1.3

Antipsychotic response is achieved when the compounds of the present invention are administered to a subject requiring such treatment as an effective oral, parenteral, or intravenous dose of from 0.01 to 50 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the aforesaid compound. It is to be further understood that the dosages set forth herein are exemplary only and they do not, to any extent, limit the scope or practice of the invention.

Some of the compounds of the present invention are also useful as analgetics due to their ability to alleviate pain in mammals. The analgetic utility is demonstrated in the phenyl p-quinone writhing assay in mice, a standard assay for analgesia: Proc. Soc. Exptl. Biol. Med., 95:729 (1957). Thus, for instance, the subcutaneous dose effecting an approximately 50% inhibition of writhing

(ED_{50}) in mice produced in this assay is as shown in Table 2.

TABLE 2

COMPOUND	INHIBITION OF PHENYLQUINONE INDUCED WRITHING ED_{50} mg/kg, sc
1-[4-[3-[4-(1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone	0.06
1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone	0.17
1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone	0.03
Propoxyphene (standard)	3.9
Pentazocine (standard)	1.3

Analgesia is achieved when the compounds of the present invention are administered to a subject requiring such treatment as an effective oral, parenteral, or intravenous dose of from 0.01 to 100 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the aforesaid compound. It is to be further understood that the dosages set forth herein are exemplary only and that they do not, to any extent, limit the scope or practice of the invention.

Effective amounts of the compounds of the present invention can be administered to a subject by any one of several methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions.

The compounds of the present invention, while effective themselves, can be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization, increased solubility, and the like. Preferred pharmaceutically acceptable addition salts include salts of mineral acids, for example, hydrochloric acid, sulfuric acid, nitric acid, and the like; salts of monobasic carboxylic acids, for example, acetic acid, propionic acid, and the like; salts of dibasic carboxylic acids, for example, maleic acid, fumaric acid, and the like; and salts of tribasic carboxylic acids, such as carboxysuccinic acid, citric acid, and the like.

Effective quantities of the compounds of the invention can be administered orally, for example, with an inert diluent or with an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purposes of oral therapeutic administration, compounds of the invention can be incorporated with an excipient and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums, and the like. These preparations should contain at least 0.5% of active compound of the invention, but can be varied depending upon the particular form and can conveniently be between 4% to about 70% of the weight of the unit. The amount of active compound in such a composition is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0–300 milligrams of the active compound of the invention.

Tablets, pills, capsules, troches, and the like can also contain the following ingredients: a binder, such as microcrystalline cellulose, gum tragacanth, or gelatin; an excipient, such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, corn starch, and the like; a lubricant such as magnesium stearate or Sterores; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose; or saccharin, or a flavoring agent, such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms can contain various materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills can be coated with sugar, shellac, or other enteric coating agents. A syrup can contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes, colorings, and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compound of the invention can be incorporated into a solution or suspension. These preparations should contain at least 0.1% of active compound, but can be varied between 0.5 and about 50% of the weight thereof. The amount of active compounds in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of active compound.

Solutions or suspensions can also include the following components: a sterile diluent, such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol, or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates, or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes, or multiple dose vials made of glass or plastic.

The following examples are for illustrative purposes only and are not to be construed as limiting the invention. All temperatures are given in degrees Centigrade (° C.) unless indicated otherwise.

EXAMPLE 1

Preparation of 1-[4-[3-[4-(1H-Indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone

(A) Synthesis of 2-bromobenzoic acid 2-phenylsulfonylhydrazide

To a solution of 2-bromobenzoic acid hydrazide (132 g) in pyridine (1.2 l) cooled to about 10° with an ice bath, was added benzensulfonyl chloride (78.3 ml). After complete addition, the reaction was stirred at ambient temperature for four hours, and then poured into ice-hydrochloric acid to precipitate a yellow solid, 135 g. The material was recrystallized from isopropanol to yield 125 g of 2-bromobenzoic acid 2-phenylsulfonylhydrazide, m.p. = 154°–156° C.

(B) Synthesis of α-chloro-2-bromobenzaldehyde phenylsulfonylhydrazone

A mixture of 2-bromobenzoic acid phenylsulfonylhydrazide (125 g, 0.35 mol) and thionyl chloride (265 ml) was stirred and refluxed for 2 hours. After about 15 minutes of reflux, the solid went into solution. The reaction was permitted to cool, and then it was poured into hexane. The resultant white solid was collected to afford 124 g of α-chloro-2-bromobenzaldehyde phenylsulfonylhydrazone, m.p. =120°–122° C.

(C) Synthesis of 1-[[(phenylsulfonyl)hydrazono]-(2-bromophenyl)methyl]-4-methylpiperazine

To a stirred solution, under nitrogen, of α-chloro-2-bromobenzaldehyde phenylsulfonylhydrazone (271.1 g; 0.72 mol) in tetrahydrofuran (THF; 2 liters), was added dropwise N-methylpiperazine (159.7 g; 1.6 mol). The reaction was stirred at ambient temperature for three hours, and then permitted to stand at ambient temperature for 16 hours. The reaction was chilled in an ice bath, and then filtered to remove the piperazine hydrochloride that was formed. The filtrate was concentrated to yield a brown gum. The gum was triturated with hot acetonitrile, the mixture was cooled in an ice bath, and when cold, was filtered to remove unwanted side product. The filtrate was then concentrated to afford 392.9 g of a brown gum of crude 1-[[(phenylsulfonyl)hydrazono]-(2-bromophenyl)methyl]-4-methylpiperazine.

(D) Synthesis of 3-(4-Methyl-1-piperazinyl)-1-phenylsulfonyl-1H-indazole

A mixture of 1-[[(phenylsulfonyl)hydrazono]-(2-bromo phenyl)methyl]-4-methylpiperazine (31.0 g, 0.08 mol), copper bronze (3.1 g), K_2CO_3 (11.5 g), and dimethylformamide (500 ml), was stirred and refluxed for 1.5 hours. The reaction was poured into water and the aqueous suspension was stirred vigorously with ethyl acetate. The biphasic mixture was filtered through celite, and subsequently the layers were separated. The aqueous portion was extracted with another portion of ethyl acetate, and the combined extracts were washed (H_2O) and dried ($MgSO_4$). Concentration of the extract afforded a solid, which upon trituration with ether gave 19.7 g of solid. The solid was recrystallized from isopropanol afford 17.7 g (60%) of product, m.p. 158°–161° C. An analytical sample was obtained by another recrystallization from isopropanol (with charcoal treatment) to afford colorless crystals of the indazole, 3-(4-methyl-1-piperazinyl)-1-phenylsulfonyl-1H-indazole, m.p.=160°–161° C.

ANALYSIS

Calculated for $C_{18}H_{20}N_4O_2S$: 60.66% C 5.66% H 15.72% N.

Found: 60.45% C 5.62% H 15.61% N.

(E) Synthesis of 4-[1-(Phenylsulfonyl)-1H-indazol-3-yl]-1-piperazinecarbonitrile

To a stirred mixture of 3-(4-methyl-1-piperazinyl)-1-phenylsulfonyl-1H-indazole (237 g, 0.67 mol), K_2CO_3 (102 g, 0.74 mol) and dimethylsulfoxide (DMSO, 2000 ml), under nitrogen, was added cyanogen bromide (72 g, 0.68 mol) dissolved in DMSO (525 ml). The reaction was stirred at ambient temperature for 5.5 hours and was then poured into H_2O (7 l). The solid, which precipitated from solution, was collected by filtration and was washed well with H_2O affording 168 g (68%) of product. A 5.2 g sample was recrystallized twice from ethanol-H_2O yielding 4.0 g of 4-[1-(phenylsulfonyl)-1H-indazol-3-yl]-1-piperazinecarbonitrile, m.p. =178°–180° C.

ANALYSIS

Calculated for $C_{18}H_{17}N_5O_2S$: 58.85% C 4.66% H 19.06% N.

Found: 59.01% C 4.63% H 19.09% N.

(F) Synthesis of 3-(1-Piperazinyl)]-1H-indazole

To a stirred mixture of 4-[1-(phenylsulfonyl)-1H-indazol-3-yl]-1-piperazinecarbonitrile (163 g, 0.44 mol) in tetrahydrofuran (2.0 l) was added, dropwise, lithium aluminum hydride (880 ml; 0.88 mol of a 1M lithium aluminum hydride solution in tetrahydrofuran). After complete addition, the reaction was heated to reflux and stirred for 6 hours, stirred at ambient temperature for one hour and allowed to sit at room temperature overnight. The reaction was quenched by the careful dropwise addition of water. After no more hydrogen could be observed to evolve, the reaction was filtered and the lithium salt filter cake was washed well with tetrahydrofuran. The filtrate was combined with the filtrate of another run (all together the starting material totaled 300 g, i.e. 0.82 mol) and the combined filtrates were concentrated to afford 372 g of a yellow solid suspended in water. An attempt was made to partition the product between water and dichloromethane, but the product proved to be only slightly soluble in dichloromethane. Therefore, the biphasic product suspension was filtered through a course sintered funnel and the white product which was collected was dried afford 121 g. The two phases of the filtrate were separated and the water was extracted again with dichloromethane. All of the dichloromethane phases were combined, washed twice with water, dried with magnesium sulfate, and concentrated to afford 41 g of a brown residue. The residue was triturated with diethyl ether and filtered to afford 10 g of a beige solid, m.p. =139°–150° C. The NMR and MS spectra were consistent with the structure. Recrystallization of 10 g from toluene afforded 7.5 g of 3-(1-piperazinyl)-1H-indazole, m.p. 153°–155° C.

(G) 3-4-Methyl-1-piperazinyl)-1H-indazole

A stirred mixture of 3-(4-methyl-1-piperazinyl)-1-phenylsulfonyl-1H-indazole (13.5 g, 0.038 mol), methanol (150 ml) and 25% CH_3ONa in methanol (15.3 ml) was stirred and refluxed for 2.5 h. The reaction was concentrated to about one-tenth its volume, and water was added to the mixture, resulting in a red solution. The solution was extracted with dichloromethane, the extract washed (H_2O), dried ($MgSO_4$), and the solvent was concentrated to afford 6.6 g of a rose-colored solid. Two recrystallizations from toluene-hexane afforded 4.3 g (52%) of 3-(4-methyl-1-piperazinyl)-1H-indazole as an off-white solid, m.p.=111°–113° C.

ANALYSIS

Calculated for $C_{12}H_{16}N4$: 66.64% C 7.46% H 25.91% N. Found: 66.83% C 7.42% H 25.69% N.

(H) 4-1H-indazol-3yl)-1-piperazinecarbonitrile

To a stirred mixture of cyanogen bromide (5.3 g, 0.05 mol), K_2CO_3 (7.1 g) and dimethylsulfoxide (40 ml) was added, dropwise, 3-(4-methyl-1-piperazinyl)-1H-indazole (11.0 g, 0.051 mol) dissolved in dimethylsulfox-

ide (60 ml). The reaction was stirred at ambient temperature for 1 h, and then it was poured into water. The aqueous suspension was extracted with ethyl acetate, the ethyl acetate was washed (H_2O), dried ($MgSO_4$), and concentrated to afford 7.8 g (67%) of a yellow solid. This sample was combined with another and recrystallized twice from toluene to afford analytically pure 4-(1H-indazol-3-yl)-1-piperazinecarbonitrile as a white solid, m.p.=120°–122° C.

ANALYSIS

Calculated for $C_{12}H_{13}N_5$: 63.42% C 5.76% H.

Found: 63.04% C 5.84% H.

(I) Synthesis of 3-(1-Piperazinyl]-1H-indazole

A mixture of 4-(1H-indazol-3-yl)-1-piperazinecarbonitrile (8.0 g, 0.04 mol) and 25% $H2SO_4$ (100 ml) was stirred at reflux for 4.5 hours. The reaction was cooled in an ice bath and made basic by the dropwise addition of 50% NaOH. The basic solution was extracted with ethyl acetate. The ethyl acetate was washed with H_2O, dried with $MgSO_4$, and concentrated to afford 5.2 g (73%) of the desired compound, as a solid. The solid was recrystallized twice from toluene to afford 3.0 g of 3-(1-piperazinyl)-1H-indazole, m.p.=153°–155° C.

ANALYSIS

Calculated for $C_{11}H_{14}N_4$: 65.32% C 6.98% H 27.70% N.

Found: 65.21% C 6.99% H 27.80% N.

(J) Synthesis of 1-[4-[3-[4-(1H-Indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(1-piperazinyl)-1H-indazole (4.0 g, 0.02 mol), K_2CO_3(3 g, 0.022 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (5.3g, 0.022 mol), a few crystals of KI, and dimethylformamide (60 ml) was stirred at 90° C. for 5 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The extract was washed (brine), dried ($MgSO_4$), and the solvent was concentrated to afford a white solid, which was triturated with diethyl ether and collected to yield 7.0g of product. Two recrystallizations from absolute ethyl alcohol yielded 5.3 g (64%) of analytically pure 1-[4-[3-[4-(1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl-]ethanone, m.p.=155°–157° C.

ANALYSIS

Calculated for $C_{23}H_{28}N_4O_3$: 67.62% C 6.91% H 13.72% N.

Found: 67.45% C 6.74% H 13.56% N.

EXAMPLE 2

1-[4-[3-[4-(1,2-Benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (4.8 g, 0.02 mol), K_2CO_3 (5.2 g, 0.04 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (5.3 g, 0.022 mol), a few crystals of KI and dimethylformamide (60 ml) was stirred at 90° C. for 16 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$) and concentrated to afford a brown oil. The oil was chromatographed on a Waters Prep 500 utilizing silica gel columns and ethyl acetatediethylamine (2%), as eluent. Concentration of the appropriate fractions afforded 3.9 g of product as an off-white solid. Recrystallization from absolute ethyl alcohol afforded 2.6 g (33%) of 1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-phenyl]ethanone, m.p.=102°–104° C., as colorless needles.

ANALYSIS

Calculated for $C_{24}H_{28}N_2O_4$: 70.56% C 6.91% H 6.86% N.

Found: 70.73% C 6.93% H 6.85% N.

EXAMPLE 3

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2 benzisoxazole hydrochloride (5.1 g, 0.02 mol), K_2CO_3 (5.2 g, 0.04 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (5.3 g, 0.022 mol), and dimethylformamide (60 ml) was heated at 90° C. for 16 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$) and concentrated to afford a moist solid. Recrystallization (twice) from ethyl alcohol afforded 5.0 (58%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3methoxyphenyl]ethanone as a beige solid, m.p.=118°–120° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_4$: 67.60% C 6.38% H 6.57% N.

Found: 67.47% C 6.40% H 6.53% N.

EXAMPLE 4

1-[4-[4-[4-(1,2-Benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanol

A mixture of 3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (4.3 g, 0.018 mol), K_2CO_3 (5.5 g, 0.04 mol), and 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (5.5 g, 0.018 mol), and dimethylformamide (60 ml) was stirred and heated at 75° C. for 16 hours. The reaction was poured into water and was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and the solvent concentrated to afford 7.2 g of a beige solid. Recrystallization (twice) from ethyl alcohol yielded 3.3 g (43%) of 1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone, m.p.=99°–101° C.

ANALYSIS

Calculated for $C_{25}H_{30}N_2O_4$: 71.11% C 7.16% H 6.63% N.

Found: 70.76% C 7.24% H 6.58% N.

EXAMPLE 5

1-[4-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyohenylethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (5.1 g, 0.02 mol), K_2CO_3 (5.2 g, 0.04 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (6.6 g, 0,022 mol), and dimethylformamide (60 ml) was heated at 75° C. for 5 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and the solvent was concentrated to yield initially an oil, which solidified upon standing. The solid was triturated with hexane and collected to afford 7.7 g of the product as a waxy solid. The compound was chromatographed on a Waters Prep 500 utilizing silica gel columns and eluting with dichloromethane/methanol (5%). Concentration of the appropriate fractions yielded 5.1 g of off-white solid 1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-

piperidinyl]butoxy]-3methoxyphenyl]ethanone, which when recrystallized from ethyl alcohol yielded 3.2 g (36%) of feathery-white needles, m.p.=88°–90° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_4$: 68.16% C 6.64% H 6.36% N. Found: 67.96% C 6.49% H 6.29% N.

EXAMPLE 6

1-[4-[2-[4-(1,2-Benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone fumarate

A mixture of 3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (4.8 g, 0.02 mol), K_2CO_3 (5.2 g, 0.04 mol), 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone (5.0 g, 0.022 mol), and dimethylformamide (90 ml) was heated at 90° C. for 16 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford an oil. Upon standing, the oil solidified to afford a beige solid. The crude solid was recrystallized twice from ethyl alcohol to afford 5.9 g of an off-white solid. The solid was dissolved in ethyl acetate, and fumaric acid (1.2 g, 1.1 equiv.) was added. The mixture was heated briefly on a steam bath, and then stirred at ambient temperature for 2 hours. An initial green oil settled out and the supernatant solution was decanted. Ether was added to the decantate and 4.0 g of a white fumarate salt was collected. The salt was recrystallized twice from ethanol-ether to yield 1.7 g (17%) of 1-[4-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone fumarate, m.p.=127°–129° C.

ANALYSIS

Calculated for $C_{23}H_{26}N_2O_4.C_4H4O_4$: 63.52% C 5.92% H 5.49% N.

Found: 63.00% C 5.87% H 5.42% N.

EXAMPLE 7

1-[4-[4-[4-(1H-indazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone fumarate

A stirred mixture of 3-(1-piperazinyl)-1H-indazole (4.0 g, 0.02 mol), K_2CO_3 (5.3 g, 0.04 mol), 1-[4-(4-bromobutoxy)-3methoxyphenyl]ethanone (6.6 g, 0.022 mol), and dimethylformamide (60 ml) was heated at 75° C. for 6 hours. The reaction was poured into water, and a white solid precipitated from solution. The solid was collected and dried to afford 7.2 g of the crude product. The crude solid was recrystallized twice from ethyl alcohol to yield 4.1 g of the free base, which was converted to its fumarate salt by the addition of fumaric acid (1.1 g) to the compound dissolved in refluxing acetone. The resulting fumarate salt (5.0 g) was recrystallized from ethyl alcohol to afford 3.8 g (35%) of 1-[4-[4-[4-(1H-indazol-3-yl)-1-piperazinyl]butoxy]-3-methoxy phenyl]ethanone fumarate, as a white solid, m.p.=163°–165° C.

ANALYSIS

Calculated for $C_{24}H_{30}N_4O_3.C_4H_4O_4$: 62.44% C 6.36% H 10.40% N. Found: 62.28% C 6.62% H 10.34% N.

EXAMPLE 8

1-[4-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2 benzisoxazole hydrochloride (5.1 g, 0.02 mol), K_2CO_3 (5.2), 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone (5.0 g, 1.022 mol), and dimethylformamide (90 ml) was heated at 90° C. for 16 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and concentrated to afford 7.4 g of a yellow solid. The solid was chromatographed on a Waters Prep LC 500 utilizing dichloromethane/methanol (4%) as eluent, and subsequent concentration of the appropriate fraction afforded 4.0 g of a yellow solid. The solid was recrystallized from ethyl alcohol to yield 3.1 g (38%) of 1-[4-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone, as slightly yellow flakes, m.p.=132°–134° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_4$: 66.98% C 6.11% H 6.79% N.

Found: 66.90% C 6.20% H 6.74% N.

EXAMPLE 9

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxy-α-methylbenzenemethanol

To a stirred mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy-3-methoxyphenyl]ethanone (4.0 g, 0.0094 mol) in methanol/tetrahydrofuran (60 ml, 1:1), was added sodium borohydride (0.4 g, 0.01 mol). After an initial evolution of gas, all insolubles went into solution. The reaction was stirred at ambient temperature for 3 hours and TLC at this time showed a very slight amount of starting ketone. Therefore, another 0.1 g of sodium borohydride was added, and stirring was continued for an additional 0.5 hour. TLC now showed complete disappearance of starting material. The reaction was concentrated to an off-white residue, which was diluted with water and collected to yield 3.4 g of alcohol. This was recrystallized from toluene (twice, with a charcoal treatment) to yield 2.7 g (67%) of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methoxy-α-methylbenzenemethanol as a white solid, m.p.=136°–138° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_2O_4$: 67.27% C 6.82% H 6.54% N.

Found: 67.59% C 6.89% H 6.47% N.

EXAMPLE 10

1-[4-[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(4-piperidinyl)-1,2-benzisothiazole (3.0 g, 0.0137 mol), potassium carbonate (2.3 g, 0.0165 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (4.0 g, 0.0165 mol), potassium iodide (200 mg) and acetonitrile (100 ml) was stirred at reflux under N_2 for 24 hours. The cooled reaction was filtered and the cake was washed well with acetonitrile. The filtrate was concentrated to an oily residue, which was partitioned between water and ethyl acetate. The ethyl acetate extract was washed well with water, dried with $MgSO_4$ and concentrated to yield 6.1 g of a beige oil which solidified upon standing. The product was triturated with diethyl ether and filtered to give 4.2 g of a beige solid. The compound was recrystallized from ethyl alcohol to afford 3.5 g, and another recrystallization from ethyl alcohol (utilizing decolorizing carbon) provided 2.4 g (41%) of 1-[4-[3-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone, m.p. 93°–95° C.

ANALYSIS

Calculated for $C_{24}H_{28}N_2O_3S$: 67.90% C 6.65% H 6.60% N.

Found: 67.89% C 6.61% H 6.59% N.

EXAMPLE 11

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone

(A) Synthesis of 1-[4-(3-chloropropoxy)-3-hydroxyphenyl]ethanone

To a stirred solution of 1-[4-(3-chloropropoxy)-3 methoxyphenyl]ethanone (10.0 g, 0.041 mol) in methylene chloride (120 ml) cooled to −50° C. (dry ice-methanol) was added, dropwise, 1M boron tribromide in methylene chloride (123 ml, 0.12 mol). The temperature was kept between −40° C. and −50° C. After complete addition, the reaction was permitted to reach −30° C., and the TLC checked (ca. 15 min. after final boron tribromide was added). Saturated $NaHCO_3$ was added, dropwise, never allowing the temperature to go above 0° C. during most of the addition. When sufficient $NaHCO_3$ had been added to make the solution basic, the organic layer was collected. The layer was washed with brine, dried ($MgSO_4$), and concentrated to yield 8.1 g of dark brown oil, which solidified on standing. This was chromatographed on a Waters Prep 500 LC (2 silica columns, 2% methanol-methylene chloride as eluent). Upon concentration of the appropriate fractions, 5.8 g of a brown tacky solid were obtained. This was recrystallized from isopropyl ether (with decanting of the yellow isopropyl ether supernatant from the dark brown oily residue) to give initially 2.5 g of a yellow solid. Concentration of the mother liquor gave an additional 0.5 g, m.p.=110°–113° C.

(B) Synthesis of 1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.8 g, 0.013 mol), $NaHCO_3$ (1.1 g), several crystals of KI, 1-[4-(3-chloropropoxy)-3-hydroxyphenyl]ethanone, and acetonitrile (100 ml) was refluxed for 16 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The organic extract was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford 5.7 g of a thick yellow oil. The oil was chromatographed on a Waters Prep 500 LC on silica gel, eluting with 7% methanol/methylene chloride. Concentration of the appropriate fraction afforded a yellow oil, which upon standing yielded 3.5 g of the compound as a pale, yellow solid. The solid was recrystallized from ethyl alcohol to afford 2.7 g (50%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone as a pale yellow solid, m.p.=122°–124° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_4$: 66.98% C 6.11% H 6.79% N.

Found: 66.97% C 6.20% H 6.69% N.

EXAMPLE 12

1-[4-[3-[4-(6-Fluoro-1H-indazol-3-yl)-1-piperazinyl]-propoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(1-piperazinyl)-1H-indazole (2.3 g, 0.01 mol), K_2CO_3 (1.5 g), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (2.8 g, 0,011 mol), several crystals of KI and dimethylformamide (60 ml) was heated at 90° C. for 16 hours. The reaction was poured into H_2O, and the aqueous suspension was extracted with ethyl acetate. The ethyl acetate was washed (H_2O), dried ($MgSO_4$) and concentrated to afford 5.0 g of a yellow oil. The oil was chromatographed on a Waters Prep 500 utilizing silica gel columns and eluting with methylene chloride/methanol (7%). Concentration of the desired fractions yielded 2.0 g (46%) of an off-white solid. This sample was combined with 1.0 g of a previous sample, and this was recrystallized from toluene to afford 2.6 g of 1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone as a white solid, m.p.=135°–137° C.

ANALYSIS

Calculated for $C_{23}H_{27}FN_4O_3$: 64.77% C 6.38% H 13.14% N.

Found: 64.66% C 6.21% H 13.02% N.

EXAMPLE 13

1-[4-[4-[4-(6-Fluoro-1H-indazol-3-yl)-1-piperazinyl]-butoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(1-piperazinyl)-1H-indazole hydrochloride (5.0 g, 0.019 ml), K_2CO_3 (5.8 g) and 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (6.3 g, 0.021 mol) and dimethylformamide (80 ml) was heated at 75° C. for 6 hours. The reaction was poured into water, and an off-white solid formed from solution. The solid was collected and dried to yield 4.5 g of crude product. The compound was recrystallized from ethanol (3 times) to afford 3.0 g of an off-white solid. The solid was chromatographed on a Waters Prep 500 utilizing silica gel columns and eluting with methylene chloride/methanol (7%). Concentration of the appropriate fractions afford 2.3 g of an off-white solid, which when recrystallized from ethanol yielded 1.9 g (26%) of analytically pure 1-[4-[4-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone, m.p.=156°–158° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_4O_3$: 65.44% C 6.64% H 12.72% N.

Found: 65.38% C 6.49% H 12.60% N.

EXAMPLE 14

1-[4-[3-[4-(1H-Indazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(4-piperidinyl)-1H-indazole (3.0 g, 0.015 mol), K_2CO_3 (1.6), 1-]4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (5.3 g, 0.022 mol), a few crystals or KI and acetonitrile (100 ml) was stirred and refluxed for 16 hours. The reaction was poured into water and a white solid separated from solution. The solid was collected, dried and afforded 5.1 g of product. Recrystallization from ethanol yielded 3.6 g of the compound, which upon chromatography (preparative HPLC on silica gel, eluting with methylene chloride/-methanol-9:1) gave 3.0 g (49%) of an off-white solid. Recrystallization from ethanol afforded the analytically pure 1-[4-[3-[4-(1H-indazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone as a white solid, m.p.=171°–173° C.

ANALYSIS

Calculated for $C_{24}H_{29}N_3O_3$: 70.74% C 7.17% H 10.31% N. Found: 70.52% C 7.27% H 10.42% N.

EXAMPLE 15

1-[4-[3-[4-(6-Chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-methoxyphenyl]ethanone

A stirred mixture of 6-chloro-3-(4-piperidinyl)-1,2-benzisoxazole (4.7 g, 0.02 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl] ethanone (4.8 g, 0.02 mol), K_2CO_3 (2.8), several crystals of KI and acetonitrile (120 ml) was refluxed for 16 hours. The reaction was filtered and the filtrate was concentrated to yield a solid-oil mixture. The residue was chromatographed on a Waters Prep 500 utilizing silica columns and eluting with methylene chloride/methanol (5%). Concentration of the desired fractions yielded 3.2 g of a beige solid, which upon recrystallization from ethanol afforded 2.7 (31%) of 1-[4-[3-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone as a beige solid, m.p.=116°–118° C.

ANALYSIS

Calculated for $C_{24}H_{27}ClN_2O_4$: 65.08% C 6.14% H 6.32% N.

Found: 65.35% C 6.22% H 6.28% N.

EXAMPLE 16

1-[4-[4-[4-(6-Chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone fumarate

A stirred mixture of 6-chloro-3-(4-piperidinyl)-1,2-benzisoxazole (4.7 g, 0.02 mol), 1-[4-(4-bromobutoxy)-3methoxyphenyl]ethanone (6.0 g, 0.02 mol), K_2CO_3 (2.8) and acetonitrile (120 ml) was refluxed for 16 hours. The reaction was allowed to cool, filtered, and the filtrate was concentrated to 9.9 g of a brown oil. The oil was chromatographed on a Waters Prep 500 utilizing silica gel columns and eluting with methylene chloride/methanol (5%). Concentration of the appropriate fractions afforded 2.3 g of an off-white solid. The solid was dissolved in ethanol and fumaric acid (0.62 g, 1.1 eq) was added. Upon concentration of the ethanol, a crude, brown solid was collected, which was taken up in refluxing acetone. Upon cooling, a white solid crystallized from solution yielding 2.2 g (19%) of 1-[4-[4-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone fumarate as a white solid, m.p.=139°–141° C.

ANALYSIS

Calculated for $C_{25}H_{29}ClN_2O_4$: $C_4H_4O_4$: 60.78% C 5.80% H 4.89% N.

Found: 60.69% C 5.74% H 4.85% N.

EXAMPLE 17

1-[4-[3-[4-(5-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone

A mixture of 5-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 0.01 mole), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (2.4 g, 0.01 mole), K_2CO_3 (1.4 g), a few crystals of KI and acetonitrile (100 ml) was stirred and refluxed for 8 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed (brine), dried ($MgSO_4$), and concentrated to afford 4.0 g of a white solid. The solid was chromatographed on a Waters Prep 500 HPLC utilizing silica gel columns and eluting with methylene chloride/methanol (5%). Concentration of the appropriate fractions afforded 2.0 g (47%) of 1-[4-[3-[4-(5-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone as a white crystalline solid, m.p.=103°–105° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_4$: 67.59% C 6.38% H 6.57% N.

Found: 67.50% C 6.47% H 6.53% N.

EXAMPLE 18

6-Fluoro-3-[1-[3-(2-methoxyphenoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.45 g; 11.1 mmoles), K_2CO_3 (2.0), and 3-(2-methoxyphenoxy)propyl chloride (3.5 g, 17.4 moles) in acetonitrile (40 ml) was heated at 90° C. for 4 hr. At the end of the reaction, the solvent was removed, and the solids were dissolved into dichloromethane (100 ml). The solution was washed with water and brine, then dried over $MgSO_4$. The crude material from the solution was combined with 1.2 g of crude material prepared in the same fashion (using 0.5 g of starting material). The combined material was purified by flash chromatography on a silica gel column (49 g, eluted with 0.5% diethylamine: 1% methanol:98.5% dichloromethane, 1 l). The fractions containing the pure product were pooled and concentrated down to a light oil (3.68). This oil was treated with fumaric acid (1.14 g, 9.8 mmoles) in ethanol (13 ml). The 6-fluoro-3-[1-[3-(2-methoxyphenoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate crystals obtained weighed 4.01 g (60%), m.p.=169°–170° C.

ANALYSIS

Calculated for $C_{22}H_{25}FN_2O_3.C_4H_4O_4$: 62.39% C 5.84% H 5.60% N.

Found: 62.37% C 5.88% H 5.60% N.

EXAMPLE 19

1-[3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]phenylmethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2 benzisoxazole (2.01 g; 9.13 moles), K_2CO_3 (2.0 g), and 1-[3-(3-chloropropoxy)-4-methoxyphenyl]phenylmethanone (3.93 g; 11.3 moles) and acetonitrile (50 ml) was heated at reflux for 4 hr. At the end of the reaction, the solvent was evaporated and the residue was partitioned between water (150 ml) and dichloromethane (400 ml). The dichloromethane solution was washed with water and brine (100 ml), dried over $MgSO_4$, then concentrated to an oil. The purification was done by flash chromatography over a silica gel column (SiO_2, 40 g; eluted with dichloromethane, 300 ml; 1% methanol in dichloromethane, 850 ml). The material thus obtained as a colorless oil solidified on standing. Recrystallization from ethanol (150 ml) gave 1-[3-[3-[4-(6-fluoro-1,2-benzisoxazol- 3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]phenylmethanone as white crystals, 3.07 g (63%), m.p.=140°–141° C.

ANALYSIS

Calculated for $C_{29}H_{29}FN_2O_4$: 71.30% C 5.98% H 5.73% N.

Found: 71.09% C 5.98% H 5.73% N.

EXAMPLE 20

1-[4-[4-[4-(1H-indazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(4-piperidinyl)-1H-indazole (3.2 g, 0.016 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (5.0 g, 0.016 mol), K_2CO_3 (2.2) and acetonitrile (100 ml) was stirred and refluxed for 6 hours. The reaction was poured into water and the resulting yellow solid that formed was collected to afford 5.3 g of product. The compound was recrystallized from acetonitrile and then from ethyl acetate to yield 3.0 g (45%) of a slightly yellow solid of 1-[4-[4-[4-(1H-indazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone, m.p.=133°–135° C.

ANALYSIS

Calculated for $C_{25}H_{31}N_3O_3$: 71.23% C 7.41% H 9.97% N.

Found: 70.85% C 7.61% H 9.81% N.

EXAMPLE 21

1-[4-[2-[4-(6-Chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-chloro-3-(4-piperidinyl)-1,2 benzisoxazole (4.6 g, 0.019 mol), 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone (4.3 g, 0.019 mol), K_2CO_3 (2.8), a few crystals of KI and acetonitrile (120 ml) was refluxed for 16 hours. The reaction was filtered and the filtrate was concentrated to yield 8.0 g of yellow solid. The solid was chromatographed on a Waters Prep 500 LC (silica columns, eluting with methylene chloride/-methanol, 5%). Concentration of the appropriate fractions yielded 3.2 g of a light yellow solid, which upon recrystallization from ethyl acetate afforded 2.3 g (28%) of 1-[4-[2-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone as a pale yellow solid, m.p.=133°–135° C.

ANALYSIS

Calculated for $C_{23}H_{25}ClN_2O_4$: 64.41% C 5.88% H 6.53% N.

Found: 64.35% C 5.87% H 6.41% N.

EXAMPLE 22

3-(3-Bromopropoxy-4-methoxyphenyl)phenylmethanone

A solution of 3-hydroxy-4-methoxybenzophenone (4.6 g, 20 mmoles) in dimethylformamide (35 ml) was treated with sodium hydride (600 mg, 25 mmoles) at 0° C. for 20 minutes, then 1,3-dibromopropane (5 g, 24.7 moles) was added in one portion. The mixture was heated at 90° C. for 1 hr, and then stirred at room temperature for 2 hr. At the end of the reaction, the mixture was poured into water (500 ml) and extracted with ethyl acetate (400 ml). The ethyl acetate solution was washed with water, brine and dried over anhydrous $MgSO_4$. The solvent was removed and the crude oil was purified by flash chromatography over a silica gel column (SiO_2, 85 g; eluted with 3:1 hexane:dichloromethane, 1.6 l; 3:7 hexane:dichloromethane, 1.4 l). The pure product thus obtained weighed 4.67 g, (66%) as an oil. Recrystallization twice from isopropyl ether (500 ml) gave analytically pure 3-(3-bromopropoxy-4-methoxyphenyl)-phenylmethanone (2.42 g), m.p.=81°–83° C.

ANALYSIS

Calculated for $C_{17}H_{17}BrO_3$: 58.47% C 4.91% H.

Found: 58.63% C 4.82% H.

EXAMPLE 23

1-[3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (4.53 m, 20.5 moles), K_2CO_3 (4.5 m), 1-[3-(3-chloropropoxy)phenyl]ethanone (6.4 g, 29 moles) in acetonitrile (60 ml) was heated at reflux for 5 hr. At the end of the reaction, the solvent was removed and the residue was extracted into dichloromethane (300 ml). The inorganic insolubles were filtered off. The dichloromethane solution was concentrated to a small volume (10 ml) and purified on a flash chromatographic column (SiO_2, 75 g, eluted with dichloromethane, 900 ml; and 2% methanol in dichloromethane, 800 ml). The fractions containing the pure product were combined and concentrated to an oil (2.87 g, 35%). The oil was dissolved into ethanol and treated with a solution of fumaric acid (841 mg). Recrystallization (twice) from ethanol afforded 2.53 g of 1-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone fumarate as white crystals, m.p.=172°–174° C.

ANALYSIS

Calculated for $C_{22}H_{25}FN_2O_3.C_4H_4O_4$ 63.27% C 5.70% H 5.47% N.

Found: 63.04% C 5.63% H 5.43% N.

EXAMPLE 24

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-methylphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2 benzisoxazole hydrochloride (5.5 g, 21.6 mmoles), K_2CO_3 (3.5 gm), 1-[4-(3-bromopropoxy)-2-methylphenyl]ethanone (4.83 g, 17.8 mmoles) in dimethylformamide (25 ml) and acetonitrile (75 ml) was heated at 120° C. for 5 hr. At the end of the reaction, the solvent was removed and the residue was extracted into dichloromethane (300 ml) and the solution was washed with water and brine. The organic solution was dried and evaporated to a crude oil. The purification was done by flash chromatography over a silica gel column (80 g, eluted with dichloromethane, 1 l; 1% methanol: dichloromethane, 1.2 l; 2% methanol:dichloromethane, 1.2 l). The purest fractions were combined and afforded 2.91 g of solid. Recrystallization from dichloromethane and ethanol gave 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2methylphenyl]ethanone as off-white crystals: 2.42 g, m.p.=113°–114° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3$: 70.22% C 6.63% H 6.82% N.

Found: 70.13% C 6.63% H 6.77% N.

EXAMPLE 25

1-[2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-5-methylphenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (2.87 g, 11.23 moles), K_2CO_3 (2.5), 1-[2-(3-bromopropoxy)-5-methylphenyl]ethanone (3.74 g, 13.8 mmoles) in dimethylformamide (10 ml) and acetonitrile (50 ml) was heated at 95° C. for 6 hr. At the end of the reaction, the solvent was concentrated and the mixture was extracted into dichloromethane (300 ml). The organic solution was washed with water and brine, dried over $MgSO_4$, then concentrated down to a crude oil. The purification was done by flash chromatography

over a silica gel column (SiO_2, 60 g, eluted with 1% CH_3OH:dichloromethane: 1.2 l; 3% CH_3OH:dichloromethane: 600 ml). The material thus obtained was crystallized from a small volume of ether and hexane to provide 2.13 gm (46%) of off-white 1-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-5-methylphenyl]ethanone, m.p.=92°-93° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3$: 70.22% C 6.63% H 6.82% N.

Found: 70.21% C 6.69% H 6.81% N.

EXAMPLE 26

N-[3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]acetamide hemifumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (3.94 g, 15.4 moles), K_2CO_3 (3.67 g, 26.6 mmole), N-[3-(3-bromopropoxy)-4-methoxyphenyl]acetamide (5.56 g, 18.6 mmoles) in dimethylformamide (75 ml) and acetonitrile (100 ml) was heated at 100° C. for 3 hr. At the end of the reaction, the solvent was concentrated and the mixture was extracted into dichloromethane (500 ml). The organic solution was washed with water (500 ml) and brine (400 ml), dried, then concentrated to a crude oil. The purification was effected by flash chromatography over a silica gel column (SiO_2, 65 g, eluted with 1% CH_3OH:dichloromethane, 1.2 l; and 3% CH_3OH:dichloromethane, 500 ml). The material thus obtained weighed 2.33 g (34.3%) as an oil. This material was dissolved in ethanol and treated with a solution of fumaric acid (661 mg) in ethanol. The N-[3-[3-[4-(6-fluoro-1,2 benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4methoxyphenyl]acetamide hemifumarate was obtained as off-white crystals weighing 2.17 g, m.p.=205°-206° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_4.0.5\ C_4H_4O_4$: 62.50% C 6.05% H 8.41% N.

Found: 62.30% C 6.05% H 8.32% N.

EXAMPLE 27

6-Chloro-3-(1-piperazinyl]-1H-indazole

To a stirred suspension of 4-(6-chloro-1-phenylsulfonyl-1H-indazol-3-yl)-1-piperazinecarbonitrile (192.5 g, 0.479 mol) in dry tetrahydrofuran (3.5 1) under N_2 was added, dropwise, $LiAlH_4$ (958 ml of a 1.0M solution of lithium aluminum hydride in tetrahydrofuran; 0.958 mol). After complete addition, the reaction was heated to reflux and stirred under N_2 for 4 hours. The reaction was cooled to 4° in an ice-salt bath and the excess lithium aluminum hydride was destroyed by the careful, dropwise addition of H_2O. The mixture was stirred vigorously for an additional 30 minutes and was then filtered through a coarse sintered glass funnel. The filter cake was washed well with tetrahydrofuran (3×500 ml) and then with methanol (2×500 ml) and the filtrate was concentrated to yield 151.0 g of a beige gum. Trituration with diethyl ether afforded a solid, which was collected and dried to give 75.0 g (66%) of the desired indazole. A 4.0 g sample was recrystallized from toluene to yield 3.2 g, which was recrystallized again from toluene (utilizing decolorizing carbon) to provide 2.1 g (35%) of a beige, 6-chloro-3-(1-piperazinyl)-1H-indazole solid, m.p.=135°-137° C.

ANALYSIS

Calculated for $C_{11}H_{13}ClN_4$: 55.82% C 5.54% H 23.67% N.

Found: 55.91% C 5.54% H 23.41% N.

EXAMPLE 28

1-[4-[3-[4-(6-Fluoro-1H-indazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1H-indazole (3.5 g, 0,016 mol), K_2CO_3 (2.2 g), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (3.8 g, 0.016 mol) and acetonitrile (90 ml) was refluxed for 16 hours. The reaction was poured into water and the resulting white solid, which precipitated from solution, was collected to afford 5.5 g of the desired product. The compound was recrystallized from dimethylformamide (twice) to afford 3.0 g (44%) of 1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]ethanone as a white solid, m.p.=202°-204° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_3$: 67.75% C 6.63% H 9.88% N.

Found: 67.59% C 6.61% H 9.96% N.

EXAMPLE 29

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methylphenyl]ethanone hemifumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (3.0 g; 11.7 moles), K_2CO_3 (3.0 g), and 1-[4-(3-bromopropoxy)-3-methylphenyl]ethanone (3.19 g) in dimethylformamide (20 ml) and acetonitrile (50 ml) was heated at 95° C. for 4 hr. At the end of the reaction, the solvent was concentrated down to about 30 ml, then partitioned between water (200 ml) and dichloromethane (300 ml). The dichloromethane solution was separated and washed with water and brine, then dried over $MgSO_4$. The crude product from the evaporated solution was purified by flash chromatography over a silica gel column (SiO_2, 60 g, eluted with 1% methanol in dichloromethane, 600 ml; 2% methanol in dichloromethane, 600 ml). The material thus obtained was a light yellow oil, weight: 2.07 g (43%). This oil was dissolved in ethanol and treated with a solution of fumaric acid (585 mg) in ethanol. The 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methylphenyl]ethanone hemifumarate crystals formed on cooling at 0° C. This was collected and weighed 1.5 g, m.p.=185°-187° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3.0.5\ C_4H_4O_4$: 66.65% C 6.24% H 5.98% N.

Found: 66.69% C 6.23% H 5.95% N.

EXAMPLE 30

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.27 g, 14.8 mmoles), K_2CO_3 (3 g), 1-[4-(3-bromopropoxy)phenyl]ethanone (4.5 g, 17.5 mmoles) in acetonitrile (60 ml) was heated at reflux for 4 hr. The solvent was removed. The residue was dissolved in dichloromethane (300 ml) and washed with water and brine, then dried over $MgSO_4$. The crude product from the evaporated solution was purified by flash chromatography (SiO_2, 60 g; eluted with 1% methanol in dichloromethane, 1 liter). The purest fractions were combined

and gave 2.8 g, 48% , of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy)phenyl]ethanone, m.p.=111°–112° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_3$: 69.68% C 6.36% H 7.07% N.

Found: 69.80% C 6.38% H 7.07% N.

EXAMPLE 31

1-[4-[3-[4-(6-Chloro-1H-indazol-3-yl)-1-piperazinyl]-propoxy]-3-methoxyphenyl]ethanone

A mixture of 6-chloro-3-(1-piperazinyl)-1H-indazole (3.4 g, 0.014 mol), K_2CO_3 (2.5 g, 0.018 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (3.8 g, 0.016 mol), KI (200 mg), and acetonitrile (125 ml) was stirred at reflux under N_2 for 30 hours. After standing at room temperature for 40 hours, the reaction was filtered and the filter cake was washed well with acetonitrile. The filtrate was concentrated to an oily solid, which was partitioned between water and ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$, and concentrated to yield 6.9 g of a dark oil, which solidified after 2 days under vacuum. The product was purified by preparative HPLC (Waters Associates Prep LC/system 500 utilizing 2 silica gel columns and 6% methanol/methylene chloride as eluent) to yield 4.2 g. The material was recrystallized from ethanol to yield 3.4 g of glistening, beige, 1-[4-[3-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone crystals, m.p.=132°–134° C.

ANALYSIS

Calculated for $C_{23}H_{27}ClN_4O_3$: 62.37% C 6.14% H 12.65% N.

Found: 62.49% C 6.16% H 12.60% N.

EXAMPLE 32

1-[4-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]butoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(1-piperazinyl)-1,2-benzisothiazole (4.0 g, 0.0182 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (6.0 g, 0.0200 mol), K_2CO_3 (3.0 g, 0.0218 mol), KI (200 mg), and acetonitrile (125 ml) was stirred at reflux under N_2 for 5 hours. Most of the solvent was removed in vacuo and the resultant gummy residue was partitioned between ethyl acetate and water. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to yield 7.8 g. Purification by preparative HPLC (Waters Associates Prep LC/System 500, utilizing 2 silica gel columns and 4% methanol-methylene chloride as eluent) afforded 6.5 g of a damp, off-white solid. The product was recrystallized twice from toluene to provide 3.1 g (39%) of 1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-butoxy]-3-methoxyphenyl]ethanone as a white solid, m.p.=114°–116° C.

ANALYSIS

Calculated for $C_{24}H_{29}N_3O_3S$: 65.58% C 6.65% H 9.56% N.

Found: 65.74% C 6.66% H 9.54% N.

EXAMPLE 33

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzonitrile

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 mmoles), K_2CO_3 (2.8 g), 4-(3-bromopropoxy)-3-methoxybenzonitrile (4.0 gm,, 14.8 mmoles) in acetonitrile (70 ml) was heated at reflux for 3 hr. At the end of the reaction, the solvent was removed on a rotary evaporator. The organic material was extracted into dichloromethane (250 ml) and the inorganics were filtered off. The dichloromethane solution was concentrated to a crude oil. The purification was done by flash chromatography over a silica gel column (SiO_2, 55 gm; eluted with dichloromethane, 600 ml; 1% methanol in dichloromethane, 600 ml). The material thus obtained was crystallized from a small amount of dichloromethane. Recrystallization from ethanol (25 ml) provided 3.8 m (68%) of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzonitrile as white crystals, m.p.=107°–108° C.

ANALYSIS

Calculated for $C_{23}H_{24}FN_3O_3$: 67.47% C 5.91% H 10.26% N.

Found: 67.32% C 5.90% H 10.24% N.

EXAMPLE 34

1-[4-[4-[4-(6-Fluoro-1H-indazol-3-yl)-1-piperidinyl]-butoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1H-indazole (1.9 g, 0.0086 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (2.6 g, 0.0086 mol), K_2CO_3 (1.2 g), and acetonitrile (75 ml) was refluxed for 6 hr. The reaction was poured into water and a white solid settled from solution. This was collected, dried and afforded 3.2 g of product. The product was recrystallized from ethanol to yield 2.7 g (71%) of 1-[4-[4-[4-(6-fluoro-1H-indazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone as glistening white flakes, m.p.=158°–160° C.

ANALYSIS

Calculated for $C_{25}H_{30}FN_3O_3$: 68.32% C 6.88% H 9.56% N.

Found: 68.00% C 6.93% H 9.51% N.

EXAMPLE 35

1-[4-[3-[4-(1-Benzoyl-6-fluoro-1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone sesquifumarate

A mixture of 1-[4-[3-[4-(6-fluoro-1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone (3.2 g, 0.0075 mol) and benzoyl chloride (15 ml) was heated on a steam bath for 15 min. The reaction was allowed to cool and ether was added. The insoluble off-white compound was harvested to yield 4.4 g of the product as a hydrochloride salt. The salt was converted to free base with aqueous ammonium hydroxide, and after extractive workup with methylene chloride, 3.0 g of the free base was isolated as a white solid. The free base was dissolved in ethyl acetate and fumaric acid (0.72 g, 1.1 eq) was added and the mixture heated on the steam bath for 15 min. After standing at ambient temperature for 4 days, 2.0 g of an off-white fumarate salt was collected, while concentration of the filtrate afforded an additional 1.0 g of the salt. Recrystallization, first from ethyl acetate, and then from ethanol yielded 1.4 g (26%) of 1-[4-[3-[4-(1-benzoyl-6-fluoro-1H-indazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone sesquifumarate, m.p.=138°–140° C.

ANALYSIS

Calculated for $C_{30}H_{31}FN_4O_4.1.5C_4H_4O_4$: 61.35% C 5.29% H 7.95% N.

Found: 61.68% C 5.31% H 8.25% N.

EXAMPLE 36

1-[4-[4-[4-(6-Chloro-1H-indazol-3-yl)-1-piperazinyl]-butoxy]-3-methoxyphenyl]ethanone

A mixture of 6-chloro-[3-(1-piperazinyl)]-1H-indazole (4.0 g, 0.017 mol), K_2CO_3 (2.8 g, 0.020 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (5.7 g, 0.019 mol), KI (100 mg) and acetonitrile (125 ml) was stirred at reflux under nitrogen for 18 hrs. The cooled reaction was poured into water and the resultant off-white solid was collected by filtration and dried to yield 7.0 g. The compound was recrystallized twice from toluene to yield 6.2 g. Further purification by preparative HPLC (Waters Associates Prep LC/System 500, utilizing 5% methanol/methylene chloride as eluent and 2 silica gel columns) afforded 5.3 g of glistening, beige crystals, which were recrystallized four times from toluene to yield 3.1 g of a white solid. Analytically pure material was obtained by a subsequent recrystallization from dimethylformamide to afford 2.5 g (32%) of 1-[4-[4-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl]-butoxy]-3-methoxyphenyl]ethanone as an off-white powder, m.p.=189°–191° C.

ANALYSIS

Calculated for $C_{24}H_{29}ClN_4O_3$: 63.08% C 6.40% H 12.26% N.

Found: 62.86% C 6.57% H 12.49% N.

EXAMPLE 37

1-[4-[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]-propoxy]-3-methoxyphenyl]ethanone hemifumarate

A mixture of 3-(1-piperazinyl)-1,2-benzisothiazole (4.0 g, 0.0182 mol), K_2CO_3 (3.0 g, 0.0218 mol), KI (200 mg), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (5.3 g, 0.0200 mol), and acetonitrile (125 ml) was stirred at reflux under N_2 for 26 hours. The cooled reaction was filtered and the filter cake was washed well with acetonitrile. The filtrate was concentrated to afford 10.7 g of an oily residue, which was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$ and concentrated to yield 8.0 g of a dark oil. The oil was purified by preparative HPLC (Waters Associates Prep LC/System 500, utilizing 2 silica gel columns and 3% methanol/methylene chloride as eluent). Concentration of appropriate fractions provided 4.6 g of a red oil, which solidified upon standing. A 3.4 g sample was taken up in ethyl acetate (100 ml) and fumaric acid (0.95 g) was added. The mixture was stirred at a mild reflux for 1 hour and then at ambient for 1.5 hrs. The resultant beige solid was collected by filtration and dried to yield 4.0 g. The product was recrystallized twice from ethanol to provide 2.7 g (27%) of 1-[4-[3-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]propoxy]-3-methoxyphenyl]ethanone hemifumarate as a beige powder, m.p.=186°–188° C.

ANALYSIS

Calculated for $C_{23}H_{27}N_3O_3S.0.5\ C_4H_4O_4$: 62.09% C 6.06% H 8.69% N.

Found: 62.01% C 6.06% H 8.68% N.

EXAMPLE 38

1-[3,5-Dibromo-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.0 g, 9.0 mmoles), K_2CO_3 (1.3), and 1-[4-(3-bromopropoxy)-3,5-dibromophenyl]ethanone (2.65 g, 9.0 mmoles) and acetonitrile (50 ml) was heated at reflux for 3 hr. At the end of the reaction, the solvent was evaporated and the residue was extracted into dichloromethane (150 ml). The insolubles were filtered off. The dichloromethane solution was concentrated down to an oil. The purification was done by flash chromatography on a silica gel column (SiO_2, 47 g; eluted with dichloromethane, 300 ml; 1% methanol in dichloromethane, 600 ml). The material thus purified as a colorless oil, solidified on standing. Recrystallization from ethanol gave 1-[3,5-dibromo-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone as white crystals (2.93 g, 57%), m.p.=102°–103° C.

ANALYSIS

Calculated for $C_{23}H_{23}Br_2FN_2O_3$: 49.84% C 4.18% H 5.05% N.

Found: 49.91% C 4.11% H 4.98% N.

EXAMPLE 39

1-[4-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethoxy]-3-methoxyphenyl]ethanone

A mixture of 3-(1-piperazinyl)-1,2-benzisothiazole (4.0 g, 0.0182 mol), 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone (4.3 g, 0.0200 mol), K_2CO_3 (3.0 g, 0.0218 mol), acetonitrile (125 ml) and a catalytic amount of KI was heated to reflux and stirred under nitrogen for 24 hours. At this point, an additional amount of K_2CO_3 (1.0 g, 0.0072 mol) and alkylating agent (0.4 g, 0.0017 mol) was added to the reaction mixture and heating at reflux was resumed for 24 hours. The reaction was cooled to ambient temperature and filtered. The filter cake was washed with acetonitrile and the filtrate was concentrated to afford a dark oil. The oil was extracted with methylene chloride, and the organic extract was washed with water, dried with $MgSO_4$ and concentrated to yield 9.2 g of an oil. Purification by preparative HPLC (Waters Associates Prep LC/System 500 utilizing 2 silica gel columns and 3% methanol/methylene chloride as eluent) provided 3.8 g of a soft, beige gum, which readily solidified. The compound was recrystallized twice from ethanol to give 2.1 g (28%) of 1-[4-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethoxy]-3-methoxyphenyl]ethanone as a beige solid, m.p.=98°–100° C.

ANALYSIS

Calculated for $C_{22}H_{25}N_3O_3S$: 64.21% C 6.12% H 10.21% N.

Found: 64.05% C 6.09% H 10°–12% N.

EXAMPLE 40

6-Fluoro-3-[1-(3-phenoxypropyl)-4-piperidinyl]-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.0 g, 0.0182 mol), K_2CO_3 (3.0 g, 0.0218 mol), KI (100 mg), 3-chloropropoxybenzene (3.4 g, 0.0200 mol), and acetonitrile was stirred at reflux under nitrogen for 30 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried with $MgSO_4$ and concentrated to afford 6.2 g of a damp, beige solid. The compound was recrystallized twice from ethanol to yield (47%) of 6-fluoro-3-[1-(3-phenoxypropyl)-4-piperidinyl]-1,2-benzisoxazole as a light beige solid, m.p.=78°–80° C.

ANALYSIS

Calculated for $C_{21}H_{23}FN_2O_2$: 71.17% C 6.54% H 7.90% N.

Found: 71.00% C 6.52% H 7.81% N.

EXAMPLE 41

1-[4-[2-[4-(6-Chloro-1H-indazol-3-yl)-1-piperazinyl]ethoxy]-3-methoxyphenyl]ethanone

A mixture of 6-chloro-[3-(1-piperazinyl)]-1H-indazole (2.1 g, 0.0089 mol), K_2CO_3 (1.5 g, 0.0107 mol), KI (100 mg), 1-[4-(2-chloroethoxy)-3-methoxyphenyl]ethanone (2.2 g, 0.0098 mol) and acetonitrile (70 ml) was stirred at reflux for 48 hours under N_2. The cooled reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic extract was washed with water, dried with $MgSO_4$ and concentrated to yield 6.0 g of a light yellow oil. The oil was purified by preparative HPLC (Waters Associates prep LC/System 500, employing 2 silica gel columns and 5.5% methanol/methylene chloride as eluent). Concentration of later fractions provided 1.6 g of an off-white solid. This was combined with an additional sample (3.4 g total) and two consecutive recrystallizations from ethanol yielded 2.1 g (23%) of 1-[4-[2-[4-(6-chloro-1H-indazol-3-yl)-1-piperazinyl] ethoxy]-3-methoxyphenyl-]ethanone an off-white solid, m.p.=154°–156° C.

ANALYSIS

Calculated for $C_{22}H_{25}ClN_4O_3$: 61.61% C 5.88% H 13.06% N.

Found: 61.66% C 5.87% H 13.06% N.

EXAMPLE 42

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyhenyl]-2,2,2-trifluoroethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (1.5 g, 0.0067 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone (2.0 g, 0.0067 mol), K_2CO_3 (0.88), KI (0.1) and acetonitrile (50 ml) was stirred and refluxed for 16 h. After cooling, the reaction was poured into water and the aqueous mixture extracted with ethyl acetate. The extract was washed (H_2O), dried ($MgSO_4$), and the solvent was concentrated to an oil, which upon evacuation at high vacuum afforded 3.2 g of a waxy solid. The solid was chromatographed on a Waters preparative LC (silica columns, eluting with 3% methanol-dichloromethane). Concentration of the appropriate fractions gave 1.8 g (56%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]-2,2,2-trifluoroethanone solid, m.p.=94°–96° C.

ANALYSIS

Calculated for $C_{24}H_{24}F_4N_2O_4$: 60.00% C 5.03% H 5.83% N.

Found: 60.01% C 5.06% H 5.68% N.

EXAMPLE 43

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl]-1-piperidinyl]propoxy]-3-methylmercaptophenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (1.88 g, 8.5 mmoles), K_2CO_3 (1.8 g) and 1-[4-(3-bromopropoxy)-3-methylmercaptophenyl]ethanone (2.3 g, 7.6 mmole) in acetonitrile (100 ml) was heated at reflux for 4 hr. At the end of the reaction, the solvent was concentrated, then diluted with dichloromethane (250 ml). The insolubles were filtered off. The dichloromethane solution was concentrated to dryness as an oil. Purification was effected by flash chromatography on a silica gel column (SiO_2, 54 g, eluted with dichloromethane, 500 ml; 1% methanol:dichloromethane, 1.1 l). The purest fractions were combined to give a colorless oil which solidified to an off-white solid (2.4 g). Recrystallization from ethanol (100 ml) yielded 1-[4-[3-[4-(6-fluoro-1,2-benzoisoxazol-3-yl]-1-piperidinyl]propoxy]-3-methylmercaptophenyl]ethanone as off-white needle crystals, 2.15 g, m.p.=150°–152° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3S$: 65.14% C 6.15% H 6.33% N.

Found: 65.09% C 6.10% H 6.25% N.

EXAMPLE 44

1-[4-(3-Bromopropoxy)-3-bromophenyl]ethanone

A stirred mixture of 3-bromo-4-hydroxyacetophenone (4.5 g, 21.2 mmoles), K_2CO_3 (4 g) and 1,3-dibromopropane (7.6 g) in acetonitrile (200 ml) was heated at reflux for 2 hr. At the end of the reaction, the solvent was removed and the residue was dissolved in dichloromethane (400 ml) and filtered. The dichloromethane solution was concentrated to an oil. The oil was added to isopropyl ether and stirred to cause crystallization (4.1 g; 58%). The solid was recrystallized from isopropyl ether to give 3.5 g of 1-[4-(3-bromopropoxy)-3-bromophenyl]ethanone as glistening crystals, m.p.=83°–84° C.

ANALYSIS

Calculated for $C_{11}H_{12}Br_2O_2$: 39.31% C 3.60% H.

Found: 39.80% C 3.55% H.

EXAMPLE 45

1-[4-(3-Bromopropoxy)-3,5-dibromophenyl]ethanone

A stirred mixture of 3,5-dibromo-4-hydroxyacetophenone (3.0 g, 10.1 mmole), K_2CO_3 (2.8 g, 20.3 mmoles), 1,3-dibromopropane (4.0 g, 19.8 moles) in acetonitrile (100 ml) was heated at reflux for 5 hr. The solvent was removed. The crude product was extracted into dichloromethane (150 ml) and the insoluble inorganics were filtered off. The solution was concentrated to dryness again. Purification was carried out by flash chromatography on silica gel (45 g, SiO_2; eluted with 1:1 hexane:dichloromethane). The material thus obtained (2.8 g) was recrystallized twice from isopropyl ether to give analytically pure 1-[4-(3-bromopropoxy)-3,5-dibromophenyl]ethanone, m.p.=87°–88° C.

ANALYSIS

Calculated for $C_{11}H_{11}Br_3O_2$: 31.84% C 2.67% H.

Found: 31.97% C 2.63% H.

EXAMPLE 46

1-[4-[4-[4-(1,2-Benzisothiazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone

A stirred mixture of 3-(4-piperidinyl)-1,2-benzisothiazole (2.6 g, 0.0119 mol), 1-[4-(4-bromobutoxy)-3-methoxyphenyl]ethanone (3.9 g, 0.0131 mol), K_2CO_3 (2.0 g, 0.0143 mol), KI (200 mg) and acetonitrile (125 ml) was stirred at reflux under nitrogen for 18 hours. The reaction was cooled to ambient temperature and filtered. The filter cake was washed well with fresh acetonitrile and the filtrate was concentrated to yield a wet, brown solid. The residue was diluted with water and the aqueous suspension was extracted with methylene chloride. The organic extract was washed with water, dried with $MgSO_4$ and concentrated to afford 6.5 g of a dark oil. The oil was purified by preparative

HPLC (Waters Associates prep LC/System 500, utilizing 2 silica gel columns and 5% methanol/methylene chloride) to give 4.5 g of a beige solid. A 3.1 g (0.0071 mol) sample was taken up in absolute ethanol (80 ml) and oxalic acid (0.67 g, 0.0074 mol) was added. The solution was refluxed mildly on a steam bath for 45 minutes and was then stirred at ambient temperature for 1 hour. The resultant suspension was diluted with anhydrous ether (150 ml) and stirred for 5 minutes. The solid was collected and dried to afford 3.1 g of a light, beige solid. The salt was recrystallized from ethanol to yield 2.8 g. The compound was converted back to the free base with 50% NaOH to give 2.4 g, which was immediately recrystallized from ethanol to provide 1.5 g (29%) of 1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]-butoxy]-3-methoxyphenyl]ethanone as a beige powder, m.p.=78°–80° C.

ANALYSIS

Calculated for $C_{25}H_{30}N_2O_3S$: 68.46% C 6.91% H 6.39% N.

Found: 68.34% C 6.85% H 6.33% N.

EXAMPLE 47

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]phenylmethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10 mmoles), K_2CO_3 (2.3 g) and 1-[4-(3-bromopropoxy)-3-methoxyphenyl]phenylmethanone (3.47 g, 10 mmoles) in acetonitrile (100 ml) was heated at reflux for 3 hours. At the end of reaction, the acetonitrile was concentrated and the mixture was extracted into dichloromethane (200 ml). The insolubles were filtered off and the solvent was evaporated to an oil. Purification was carried out by flash chromatography over a silica gel column (SiO_2, 50 g; eluted with dichloromethane, 600 ml; 1% methanol:dichloromethane, 600 ml; 2% methanol: 98% dichloromethane, 600 ml). The fractions containing the pure product were combined and concentrated to give 4.24 g (87%) of an off-white solid. Recrystallization from ethanol (75 ml) gave 3.9 g of 1-[4-[3-[4-(6-fluoro-1,2-benziosoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]phenylmethanone as off-white crystals, m.p.=128°–130° C.

ANALYSIS

Calculated for $C_{29}H_{29}FN_2O_4$: 71.30% C 5.98% H 5.73% N.

Found: 71.31% C 5.99% H 5.75% N.

EXAMPLE 48

1-[4-[3-[4-(6-Fluoro-1,2-benziosoxazol-3-yl)-1-piperidinyl]propoxy]-3-bromophenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.1 g, 9.5 mmole), K_2CO_3 (2.0 g) 1-[3-bromo-4-(3-bromopropoxy)phenyl]ethanone (3.1 g, 9.2 mmoles) in acetonitrile (100 ml) was heated at reflux for 3 hours. At the end of reaction, the solvent was concentrated and the mixture was extracted into dichloromethane (200 ml). The insolubles were filtered off. The dichloromethane was concentrated again. The crude residue was purified by flash chromatography over a silica gel column (SiO_2, 49 g; eluted with dichloromethane, 500 ml; 1% methanol:dichloromethane, 600 ml; 3% methanol: 97% dichloromethane, 600 ml). The material thus obtained (3.26 g, 72%) was recrystallized from ethanol (40 ml) to give 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-bromophenyl]ethanone as light yellow crystals (3.0), m.p.=126°–128° C.

ANALYSIS

Calculated for $C_{23}H_{24}BrFN_2O_3$: 58.12% C 5.09% H 5.89% N.

Found: 57.64% C 5.35% H 5.55% N.

EXAMPLE 49

3-[1-[3-[4-(1-Ethoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole hydrochloride

To a mixture of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-α-methylbenzenemethanol (3.8 g, 0.089 mol) in pyridine (25 ml) was added acetic anhydride (5 ml). The mixture was warmed briefly on the steam bath to effect solution, and then the reaction was allowed to stand at ambient temperature for 16 hours. Most of the pyridine was evaporated under reduced pressure and the resultant oil was diluted with water. The aqueous solution was made basic with dilute NaOH, and subsequently extracted with ethyl acetate. The organic extract was washed (water), dried ($MgSO_4$), and the solvent concentrated to give 3.7 g of the O-acetyl derivative as a colorless oil. The compound was dissolved in diethyl ether and ethereal HCl was added to precipitate a gum-like hydrochloride salt, which upon treatment with refluxing ethyl acetate afforded 3.4 g of a crystalline salt, m.p. 143°–145° C. Attempting to recrystallize the salt from ethanol:diethyl ether resulted in displacement of the acetate to afford the ethyl ether. The salt of this product (2.8 g) was recrystallized from ethanol:diethyl ether to yield 2.1 g (48%) of 3-[1-[3-[4-(1-ethoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole hydrochloride, m.p.=139°–141° C.

ANALYSIS

Calculated for $C_{26}H_{33}FN_2O_4.HCl$: 63 . 34% C 6.95% H 5.68% N.

Found: 63.06% C 6.80% H 5.63% N.

EXAMPLE 50

3-[1-[3-[4-(1-Acetoxyethyl)-2-methoxyphenoxy]-propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole fumarate

A mixture of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-3-methoxy-α-methylbenzenemethanol (4.8 g, 0.011 mol) in pyridine (45 ml) was warmed briefly to effect solution and then acetic anhydride (6.3 ml) was added. The reaction stood at ambient temperature for 16 hours, was concentrated in vacuo, and the colorless oil that remained was dissolved in water. The aqueous solution was made basic with saturated K_2CO_3 solution, and the mixture was extracted with diethyl ether. The extract was washed (water), dried ($MgSO_4$) and concentrated to afford 5.2 g of a thick, colorless oil. The oil (4.8 g) was dissolved in anhydrous diethyl ether and fumaric acid (1.2 g, 0.01 mol) was added. The mixture was stirred at ambient temperature for 4 hours, and then was permitted to stand at ambient temperature for 16 hours. The resultant white, 3-[1-[3-[4-(1-acetoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2benzisoxazole fumarate was collected and afforded 3.0 g of material. The filtrate was treated with an additional amount of fumaric acid (0.3) and 0.9 g more of 3-[1-[3-[4-(1-acetoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole fumarate was harvested. The two batches were combined

and recrystallized from acetonitrile (twice) to yield 2.3 g (43%) of the acetate, m.p.=150°–152° C.

ANALYSIS

Calculated for $C_{26}H_{31}FN_2O_3.C_4H_4O_4$: 61.43% C 6.01% H 4.78% N.

Found: 61.06% C 5.87% H 4.73% N.

EXAMPLE 51

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]pentanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 0.01 mole), K_2CO_3 (3 g), 1-[4-(3-bromopropoxy)-3-methoxyphenyl]pentanone (3.7 g, 0.0113 mole) in acetonitrile (140 ml) was heated at reflux for 4 hours. At the end of the reaction, the mixture was cooled and filtered. The filtrate was concentrated to an oil. Purification was performed by flash chromatography over a silica gel column (SiO_2, 55 g; eluted with 1% methanol in dichloromethane, 600 ml; 3% methanol: 97% dichloromethane, 400 ml). The fractions containing pure product were pooled and concentrated to a solid (4.3 g, 91%). Recrystallization from ethanol (10 ml) gave a powdery solid of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]pentanone (3.22), m.p.=79°–80° C.

ANALYSIS

Calculated for $C_{27}H_{33}FN_2O_4$: 69.21% C 7.10% H 5.98% N.

Found: 69.00% C 6.94% H 6.39% N.

EXAMPLE 52

2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-N-methylbenzenamine hemifumarate

A mixture of 6-fluoro-3-(4-piperdinyl)-1,2-benzisoxazole (2.5 g, 0.0114 mol), K_2CO_3 (1.8 g, 0.0130 mol), 4-(3-chloropropoxy)-2-methylaminobenzene (2.4 g, 0.0120 mol) and acetonitrile (100 ml) was stirred at reflux for 18 hours. The reaction was cooled to ambient temperature and was poured into water. The aqueous mixture was extracted with ethyl acetate and the ethyl acetate extract was washed with water, dried with $MgSO_4$, and concentrated to yield 4.1 g of a brown oil. The oil was purified by preparative HPLC (Waters Associates prep LC/System 500, utilizing 2 silica gel columns and eluting with 4% methanol-methylene chloride). Concentration of appropriate fractions yielded 2.45 g of a beige oil. The product was taken up in ethyl acetate (50 ml) and fumaric acid (0.78 g) was added. The mixture was stirred at mild reflux for 45 minutes and then at ambient temperature for 1.5 hours. The product was isolated by vacuum filtration to provide 2.5 g of a pale yellow solid. Recrystallization from ethanol afforded 2.0 g (40%) of 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-N-methylbenzenamine hemifumarate as beige crystals, m.p.=180°–182° C.

ANALYSIS

Calculated for $C_{22}H_{26}FN_3O_2.0.5C_4H_4O_4$: 65.28% C 6.40% H 9.52% N.

Found: 65.08% C 6.35% H 9.45% N.

EXAMPLE 53

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]propanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.8 g, 15.2 mmoles), K_2CO_3 (3), 1-[4-(3-bromopropoxy)-3-methoxyphenyl]propanone (4.6 g, 18.2 mmoles) in acetonitrile (100 ml) was heated at reflux for 2 hours. At the end of the reaction, the mixture was filtered and the solvent was concentrated and the residue was extracted into dichloromethane (300 ml). The dichloromethane was filtered and concentrated again. The crude material (6.4) was purified by flash chromatography over a silica gel column (SiO_2, 50 g; eluted with dichloromethane, 700 ml; 1% methanol in dichloromethane, 1.4 l). The material thus purified (weight: 2.87 g, 51%) was recrystallized from ethanol (25 ml) to give 2.13 g of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl]propanone as beige colored crystals, m.p.=118°–119° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_4$: 68.16% C 6.64% H 6.36% N.

Found: 68.32% C 6.63% H 6.29% N.

EXAMPLE 54

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzamide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10.0 mmoles), K_2CO_3 (2.0 g) and 4-(3-bromopropoxy)-3-methoxybenzamide (2.32 g, 8.0 moles) in acetonitrile (80 ml) was heated at reflux for 5 hours. At the end of the reaction the solvent was evaporated. The residue was extracted into dichloromethane. The inorganic insolubles were filtered off. The dichloromethane was concentrated again. The crude residue was purified by flash chromatography over a silica gel column (55 g, SiO_2; eluted with 1% methanol in dichloromethane, 1 l; 2% methanol in dichloromethane, 1 l). The material thus obtained weighed 2.93 g (84%) as white crystals. Recrystallization from hot ethanol (60 ml) gave 2.2 g of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-benzamide as white crystals, m.p.=163°–164° C.

ANALYSIS

Calculated for $C_{23}H_{26}FN_3O_4$: 64.62% C 6.13% H 9.83% N.

Found: 64.20% C 6.06% H 9.71% N.

EXAMPLE 55

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy-]-3-(methylamino)phenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.3 g, 0.0103 mol), K_2CO_3 (1.4 g, 0.0103 mol), 1-[4-(3-chloropropoxy)-3-(methylamino)phenyl]ethanone (2.5 g, 0.0103 mol), KI (0.10), and acetonitrile (100 ml) was stirred at reflux under nitrogen for 23 hours. The reaction was cooled to ambient temperature, poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed twice with water, dried with $MgSO_4$ and was concentrated to yield 4.8 g of a damp, brown solid. The compound was isolated by preparative HPLC (Waters Associates prep LC/System 500, utilizing 2 silica gel columns and 4% methanol-methylene chloride as eluent). Concentration of appropriate fractions afforded 2.4 g. Recrystallization from ethanol gave 2.1 g of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-(methylamino)phenyl]ethanone as a beige solid, m.p.=151°–153° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_3$: 67.75% C 6.63% H 9.88% N.

Found: 67.83% C 6.76% H 9.90% N.

EXAMPLE 56

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-ethoxyphenyl]ethanone

A suspension of NaH (0.28 g of a 50% oil dispersion, 0.0059 mol) in dimethylformamide (20 ml) was cooled to 4° C. in an ice bath. To this was added, dropwise, 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone (2.3 g, 0.0056 mol) dissolved in dimethylformamide (40 ml). After total addition, the mixture was stirred under nitrogen for 1 hr. keeping the temperature below 10° C. A solution of bromoethane (1.3 g, 0.0118 mol) dissolved in dimethylformamide (15 ml) was then added, dropwise, to the reaction mixture. Stirring under nitrogen was continued for 3 hours allowing the temperature to slowly rise to ambient temperature. The reaction was cooled in an ice bath, water was added and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$, and was concentrated to yield 3.9 g of a damp, beige solid. The solid was triturated with diethyl ether and filtered to yield 1.5 g. This was combined with an additional sample (3.5 g total), and recrystallization from ethanol provided 3.0 g (57%) of glistening, beige crystals of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-ethoxyphenyl]ethanone, m.p.=112°–114° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_4$: 68.16% C 6.64% H 6.36% N.

Found: 68.10% C 7.03% H 6.35% N.

EXAMPLE 57

1-[4-(3-Bromopropoxy)-3-(methylmercapto)phenyl]ethanone

A mixture of 1-[4-hydroxy-3-(methylmercapto)-phenyl]ethanone (5.4 g; 0.03 mole), K_2CO_3 (4.2 g), 1,3-dibromopropane (8 g, 0.039 mole) in acetonitrile (150 ml) was heated at reflux for 3 hours and stirred at room temperature overnight. Acetonitrile was removed at reduced pressure and the residue was extracted into dichloromethane (250 ml). Insolubles were filtered off. The dichloromethane solution was concentrated. The crude product was purified on a silica gel column (SiO_2, 100 g; eluted with 3:2 hexane:dichloromethane, 1.6 l). The compound crystallized upon concentration, and the product (3.5 g, 39%) was recrystallized from ethanol (40 ml) to yield 1-[4-(3-bromopropoxy)-3-(methylmercapto)phenyl]ethanone as white needles, 2.0 g; m.p.=120°–122° C.

ANALYSIS

Calculated for $C_{12}H_{15}BrO_2S$: 47.53% C 4.99% H.

Found: 47.74% C 4.91% H.

EXAMPLE 58

4-(3-Bromopropoxy)-3-methoxybenzonitrile

A mixture of 4-hydroxy-3-methoxybenzonitrile (7.5 g, 50 mmoles), K_2CO_3 (12.5), and 1,3-dibromopropane (15 g, 75 moles) in acetonitrile (100 ml) was heated at reflux for 3 hours and left standing at room temperature overnight. The solvent of the reaction was removed on a rotary evaporator, and the crude solid was extracted into methylene chloride (500 ml). The insolubles were filtered off. The dichloromethane solution was concentrated and the material was purified on a flash chromatography column (SiO_2, 105 g; eluted with 2:3 dichloromethane:hexane, and then with dichloromethane). The desired product thus purified weighed 7.74 g (52%). Recrystallization twice from ethanol gave analytically pure 4-(3-bromopropoxy)-3-methoxybenzonitrile, m.p.=99°–101° C.

ANALYSIS

Calculated for $C_{11}H_{12}BrNO_2$: 48.91% C 4.48% H 5.19% N.

Found: 49.49% C 4.47% H 5.21% N.

EXAMPLE 59

1-[4-(3-Bromopropoxy)-3-methylphenyl]ethanone

A mixture of 4-hydroxy-3-methylacetophenone (14.5 g, 96 moles), K_2CO_3 (17.5 g, 144 mmoles), and 1,3-dibromopropane (30 g, 144 mmoles) in acetonitrile (400 ml) was heated at reflux for 6 hours. At the end of the reaction, the solvent was removed on a rotary evaporator, and the crude solid was extracted into dichloromethane (750 ml). The insoluble inorganics were filtered off. The dichloromethane solution was concentrated again to a crude oil (34.5 g). Purification was effected by flash chromatography over a silica gel column (SiO_2, 150 g; eluted with 7:3 hexane:dichloromethane, 2 l; and dichloromethane 2 l). The material thus purified weighed 14.6 g (56%) and was recrystallized from ethanol. Recrystallization again from ethanol gave analytically pure 1-[4-(3-bromopropoxy)-3-methylphenyl]ethanone, m.p.=59°–61° C.

ANALYSIS

Calculated for $C_{12}H_{15}BrO_2$: 53.15% C 5.58% H.

Found: 53.35% C 5.52% H.

EXAMPLE 60

1-[4-(3-Bromopropoxy)-3-methoxyphenyl]phenylmethanone

A mixture of 1-(4-hydroxy-3-methoxyphenyl)phenylmethanone (14 g, 61.4 mmoles), K_2CO_3 (13 g, 92.1 mmoles), and 1,3-dibromopropane (28 g, 86 moles) in acetonitrile (400 ml) was heated at reflux for 4 hours. The reaction was followed by thin layer chromatography. At the end of the reaction, the inorganics were filtered off and the solvent was removed on a rotary evaporator. The residue was purified on a flash chromatographic column (SiO_2, 140 g, eluted with 4:1 hexane:dichloromethane, 1.2 l) to give a partially solidified material: 15.44 g (72%). Recrystallization twice from ethanol gave 2.84 g of 1-[4-(3-bromopropoxy)-3-methoxyphenyl]phenylmethanone as white crystals, m.p.=88°–89° C.

ANALYSIS

Calculated for $C_{17}H_{17}BrO_3$: 58.47% C 4.91% H.

Found: 59.03% C 4.87% H.

EXAMPLE 61

N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide

(A)

N-[2-(3-phenylsulfonyloxypropxoy)phenyl]acetamide

To a solution of N-[2-(3-hydroxypropoxy)phenyl]-acetamide (Example 113) (7.5 g, 0,036 mol) in pyridine (90 ml), cooled to 0° C., was added p-toluenesulfonyl chloride (13.6 g, 0.056 mol). After the tosyl chloride went into solution, the reaction was then allowed to stand at 5° C. for 16 hours. The reaction was poured

onto ice, and a brown oil settled. The aqueous supernatant was decanted from the oil, and the residual oil taken up in diethyl ether. The diethyl ether was washed with cold (5° C.) 3N HCl and then with brine. The organic layer was dried ($MgSO_4$), and concentrated to afford a thick, brown oil, 5.3 g.

(B)

N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.4 g, 0.016 mol), N-[2-(3-phenylsulfonyloxypropxoy)phenyl]acetamide (5.3 g, 0.016 mol), K_2CO_3 (2.2 g), and acetonitrile (50 ml) was stirred and refluxed for 5 hours. The reaction was poured into water, and the aqueous suspension was extracted with ethyl acetate. The ethyl acetate was washed (water and brine), dried ($MgSO_4$) and the solvent was concentrated to afford 6.0 g of a thick, brown oil. The oil was chromatographed on a Waters Prep 500 LC on silica gel. Concentration of the appropriate fractions afforded 3.0 g of a beige solid. This was recrystallized from ethyl acetate to yield (with concentration of the mother liquors) 2.2 g (33%) of N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide as a beige solid, m.p.=118°–120° C.

ANALYSIS

Calculated for $C_{23}H_{26}FN_3O_3$: 67.14% C 6.37% H 10.21% N.

Found: 67.06% C 6.43% H 10.23% N.

EXAMPLE 62

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-dimethylaminophenyl]ethanone

(A)

1-[4-(3-Chloropropoxy)-3-dimethylaminophenyl]ethanone

To a suspension of sodium hydride (2.3 g, 0.0485 mol of 50% oil dispersion) with dimethylformamide (75 ml), and cooled to 3° in an ice-salt bath and under a stream of nitrogen was added, dropwise, 1-(4-hydroxy-3-dimethylaminophenyl)ethanone (8.7 g, 0.0485 mol) dissolved in dimethylformamide (150 ml) so that the temperature did not go over 7°. After the addition was over, the bath was removed and the reaction was stirred at ambient temperature for 45 minutes. The ice bath was reapplied and a solution of 1-bromo-3-chloropropane (8.4 g, 0.0534 mol) in dimethylformamide (25 ml) was added dropwise. After the addition was complete, the reaction was stirred for 18 hours at ambient temperature under nitrogen. The reaction was chilled to 7° in an ice bath and water (200 ml) was carefully added. After stirring for 5 minutes, the aqueous mixture was extracted with ethyl acetate (5×200 ml). The ethyl acetate extract was washed with water (2×50 ml), dried with $MgSO_4$, and concentrated to yield 22.2 g of a black oily liquid. The compound was purified by prep HPLC, and combination of appropriate fractions gave 5.0 g of brown oil.

(B)

1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl>-1-piperidinyl]propoxy]-3-dimethylaminophenyl]ethanone

A mixture of 1-[4-(3-chloropropoxy)-3-dimethylaminophenyl]ethanone (2.9 g, 0.0113 mol), 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.5 g, 0.0113 mol), K_2CO_3 (1.7 g, 0.0122 mol), KI (200 mg) and acetonitrile (125 ml) was stirred at reflux for 18 hours. The cooled reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried with magnesium sulfate and concentrated to yield 5.3 g of an amber oil. The compound was purified by preparative HPLC (Waters Associates prep LC/System 500 utilizing 2 silica gel columns) and concentration of appropriate fractions provided 1.65 g (33%). After combining with two additional samples, the compound (3.4 g, 7.74 mmol total) was taken up in ethyl acetate and fumaric acid (0.90 g, 7.75 mmol) was added. The mixture was stirred at a mild reflux for 30 minutes and then for 1 hour at ambient temperature. The reaction was left to stand overnight and was then filtered to give 3.6 g. The compound was recrystallized twice from ethanol to provide 2.3 g and once from acetonitrile to yield 1.9 g of the compound as a fumarate salt. The compound was converted to the free base by suspending it in dilute NaOH and extracting with dichloromethane. After washing the dichloromethane extract with water and drying with $MgSO_4$, the solvent was removed in vacuo to give 1.4 g (14%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-dimethylaminophenyl]ethanone as a beige solid, m.p.=94°–96° C.

ANALYSIS

Calculated for $C_{25}H_{30}FN_3O_3$: 68.32% C 6.88% H 9.56% N.

Found: 67.74% C 6.74% H 9.40% N.

EXAMPLE 63

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-methoxyphenyl]ethanone hydrochloride

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.4 g, 0.02 mol), 1-[4-(3-chloropropoxy)-2-methoxyphenyl]ethanone (4.8 g, 0.02 mol), K_2CO_3 (2.8), KI (200 mg) and acetonitrile (110 ml) was stirred and refluxed for 16 hours. The reaction was filtered and the filtrate concentrated to afford 9.0 g of a brown oil. The oil was taken up in acetone and fumaric acid (2.5 g, 0.022 mol) was added. The mixture was heated to reflux and then it was stirred at ambient temperature for 1 hour. The resultant fumarate salt (7.0 g) was collected and then reversed to the free base with aqueous sodium hydroxide to afford 4.6 g of a soft solid. The solid was flash chromatographed on silica gel with dichloromethane-methanol (10%) as eluent, and after concentration of the appropriate fractions afforded 3.6 g of an off-white solid. The solid was dissolved in anhydrous ether and ethereal HCl was added to precipitate 3.3 g of the hydrochloride salt. The salt was recrystallized from ethanol to afford 3.3 g of product. Occluded alcohol was removed to yield 2.8 g (29%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-methoxyphenyl]ethanone hydrochloride, m.p.=193°–195° C.

ANALYSIS

Calculated for $C_{24}H_{28}ClFN_2O_4$: 62.27% C 6.10% H 6.05% N.

Found: 61.88% C 5.90% H 5.96% N.

EXAMPLE 64

1-[4-(3-Chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone

(A) 4-(3-Chloropropoxy)-3-methoxybenzoic acid

To a stirred suspension under nitrogen of sodium hydride (6.4 g, 0.13 mol, of about 50% oil dispersion-

ether washed) in tetrahydrofuran (220 ml) was added pyrazole (4.4 g, 0.06 mol) in tetrahydrofuran (60 ml), dropwise. After complete addition, the reaction was stirred for about 15 minutes, and then 4-(3-chloropropoxy)-3-methoxybenzaldehyde (24.5 g, 0.107 mol) was added. The nitrogen was stopped and air was sparged into the reactor for about 3 hours. The reaction was then allowed to stir at ambient temperature open to the atmosphere for 16 hours. Water was added, the reaction was cooled in an ice bath, and concentrated hydrochloric acid (25 ml) was added dropwise. More water was added and the yellow solid that separated was collected to afford 16.2 g of product. The filtrate was then extracted with ethyl acetate to afford an additional 9.3 . The samples were combined and recrystallized from acetonitrile to yield 12.6 g of a light, yellow solid, m.p.=154°–156° C. A 4.0 g sample was recrystallized from acetonitrile to yield 2.6 g of a yellow solid. This was combined with 0.4 g from another sample and recrystallized again from acetonitrile with charcoal treatment to afford 2.0 g of 4-(3-chloropropoxy)-3-methoxybenzoic acid as a yellow solid, m.p.=157°–159° C.

ANALYSIS

Calculated for $C_{11}H_{13}ClO_4$: 54.00% C 5.35% H.
Found: 54.65% C 5.34% H.

(B) 4-(3-Chloropropoxy)-3-methoxybenzoyl chloride

To a mixture of 4-(3-chloropropoxy)-3-methoxybenzoic acid (2.4 g, 0.01 mol) in dichloromethane (5 ml) was added thionyl chloride (0.9 ml, 0.012 mol) dissolved in dichloromethane (5 ml). The reaction was stirred and refluxed for 1 hour, and then the dichloromethane was removed in vacuo to leave a dark oil. The oil was triturated with hexane and the solid that formed while scratching with a glass rod was collected to afford 1.6 g of 4-(3-chloropropoxy)-3-methoxybenzoyl chloride, m.p.=60°–63° C.

(C)

1-[4-(3-Chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone

To a stirred mixture of 4-(3-chloroproxy)-3-methoxybenzoyl chloride (10.0 g, 0.038 mol) in methylene chloride (55 ml) cooled to −70° C., there was condensed into a reactor bromotrifluoromethane (70 g, 0.047 mol). There was then added to the reactor hexamethylphosphoroustriamide (9.4 g, 0.041 mol) dissolved in dichloromethane (7 ml). The first 90% was added quite rapidly, and the remainder at a slower rate. After complete addition, the reaction was stirred at −70° C. to −65° C. for an additional hour. The reaction mixture was allowed to come to room temperature. An equal volume of hexane was added and the layers were separated. The lower layer was extracted with hexane and then with diethylether. The extracts were combined and concentrated to yield 5.6 g of a thick, colorless oil. The oil was chromatographed on a Waters Prep 500 LC utilizing two silica gel columns and eluting with 20% ethyl acetate-hexane. Concentration of appropriate fractions gave 2.7 g of a light oil, which after evacuation at high vacuum solidified to a waxy, white solid (2.4) of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]-2,2,2-trifluoroethanone.

EXAMPLE 65

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxy-α-methylbenzene methanol

(A) 1-[4-(3-chloropropoxy-3-hydroxyphenyl]ethanone

A mixture of 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (10.0 g, 0.0412 mol) and concentrated H_2SO_4 (50 ml) was stirred at 65° for 23 hours. The cooled reaction was poured into 250 g of ice and was stirred vigorously for 10 minutes. The aqueous mixture was extracted with dichloromethane (CH_2Cl_2) and the resultant dichloromethane extract was washed well with 5% sodium hydroxide. The basic phases were combined and washed with dichloromethane. The aqueous mixture was cooled in an ice bath and concentrated hydrochloric acid was added until a precipitate formed. The product was isolated by filtration and dried to yield 3.1 of a light brown solid. This was combined with an additional sample (5.0 g total) and two consecutive recrystallizations from toluene provided 3.4 g (22%) of 1-[4-(3-chloropropoxy)-3-hydroxyphenyl]ethanone as a beige solid, m.p.=101°–103° C.

ANALYSIS

Calculated for $C_{11}H_{13}ClO_3$: 57.78% C 5.73% H.
Found: 58.17% C 5.66% H.

(B) 4-(3-chloropropoxy)-3-hydroxy-α-methylbenzene methanol

To a flask charged with sodium borohydride (1.5 g, 0.0394 mol) under nitrogen and chilled to 10° was added, slowly, a solution of 1-[4-(3-chloropropoxy)-3-hydroxyphenyl]ethanone (6.0 g, 0.0262 mol) dissolved in ethanol-tetrahydrofuran (120 ml, 2:1). After total addition, the ice bath was removed and the reaction was stirred at ambient temperature for 3 hours. An additional amount of sodium borohydride (0.2 g, 0.0053 mol) was carefully added. After stirring at ambient temperature for one hour, the solvent was removed in vacuo. The resultant solid residue was diluted with water (100 ml) and left overnight. The product was isolated by vacuum filtration yielding 3.8 g. Two consecutive recrystallizations from toluene provided 3.3 g (55%) of 4-(3-chloropropoxy)-3-hydroxy-α-methylbenzene methanol as a light brown solid, m.p.=107°–109° C.

ANALYSIS

Calculated for $C_{11}H_{15}ClO_3$: 57.27% C 6.55% H.
Found: 57.60% C 6.43% H.

(C)

4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxy-α-methylbenzene methanol

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.3 g, 0.0195 mol), 4-(3-chloropropoxy)-3-hydroxy-α-methylbenzenemethanol (4.5 g, 0.0195 mol), KI (200 mg), $NaHCO_3$ (1.8 g, 0.0215 mol) and CH_3CN (125 ml) was stirred at reflux under nitrogen for 24 hours. The cooled reaction was filtered and the filter cake was washed with CH_3CN. The filtrate was concentrated to afford an oily residue, which was partitioned between water and ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$, and concentrated to yield 8.6 g of a dark oil. The oil was purified by preparative HPLC (Waters Associates prep LC/system 500) to yield 5.0 g. The compound was recrystallized twice from ethanol to provide 3.9 g (49%) of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-

piperidinyl]propoxy]-3-hydroxy-α-methylbenzene methanol as a light beige solid, m.p.=142°–144° C.

ANALYSIS

Calculated for $C_{23}H_{27}FN_2O_4$: 66.65% C 6.57% H 6.76% N.

Found: 66.68% C 6.35% H 6.72% N.

EXAMPLE 66

2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline dihydrochloride

(A) 2-(3-chloropropoxy) aniline

To a stirred suspension of sodium hydride (11.0 g, 0.23 mol of a 50% oil dispersion) in dimethylformamide (250 ml), under nitrogen, was added, dropwise, 2-aminophenol (25.0 g, 0.23 mol) dissolved in dimethylformamide (125 ml). After complete addition, the reaction was stirred at ambient temperature for 1 hour, and then it was cooled to 5° C. (ice bath). 3-Chloro-1-bromopropane (36.2 g, 0.23 mol) in dimethylformamide (50 ml) was added, dropwise, so that the temperature did not go above 8° C. The reaction was stirred for 4 hours and then permitted to stand at ambient temperature for 16 hours. The reaction was poured into water and extracted with ethyl acetate. The ethyl acetate was washed (water), dried ($MgSO_4$), and the solvent concentrated to afford 25.4 g of a reddish, dark oil. About 12.0 g of the oil was chromatographed on HPLC columns. Concentration of the largest fractions gave 5.4 g of 2-(3-chloropropoxy) aniline as an oil.

(B)

2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline dihydrochloride

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.8 g, 0.022 mol), 2-(3-chloropropoxy)aniline (4.0 g, 0,022 mol), K_2CO_3 (4.1 g, 0,022 mol), KI (0.2 g), and acetonitrile (100 ml) was stirred and refluxed for 10 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford 9.0 g of a red solid. The solid was triturated with diethyl ether to yield 3.0 g of a beige solid. This sample was combined with a sample (1.1 g) from another run, and a hydrochloride salt was prepared by dissolving the free base in ethanol and then adding ethereal HCl. The resultant salt (3.5 g) was recrystallized twice from methanol-diethyl ether to afford 2.6 g (22%) of 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]aniline dihydrochloride as a brown solid, m.p.=253°–255° C.

ANALYSIS

Calculated for $C_{21}H_{24}FN_3O_2.2HCl$: 57.02% C 5.92% H 9.50% N.

Found: 56.68% C 5.71% H 9.35% N.

EXAMPLE 67

N-[5-Acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy-]phenyl acetamide

(A) Preparation of 1-[3-acetylamino-4-(3-chloropropoxyphenyl]ethanone

A stirred mixture of 1-[3-acetylamino-4-hydroxyphenyl]ethanone (7.7 g, 0.04 mol), K_2CO_3 (5.7), 3-chloro-1-bromopropane (8.9 g, 0,056 mol) and acetone (100 ml) was refluxed for 16 h. The reaction was allowed to cool to ambient temperature and filtered. Concentration of the filtrate yielded 8.5 g of a white solid. The solid was recrystallized from toluene and then from ethanol to afford 6.5 g of an off-white solid. A 3.3 g sample of this material was flash chromatographed on silica gel with ethyl acetate as eluent. Concentration of the appropriate fractions afforded 2.8 g of a solid. The solid was recrystallized from toluene and then from ethanol-water to yield 2.2 g (51%) of a solid, m.p.=124°–126° C.

ANALYSIS

Calculated for $C_{13}H_{16}ClNO_3$: 57.89% C 5.98% H 5.19% N.

Found: 57.08% C 5.85% H 5.13% N.

(B)

N-[5-acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.4 g, 0.02 mol), 1-[3-acetylamino-4-(3chloropropoxy)phenyl]ethanone (5.5 g, 0.0205 mol), K_2CO_3(2.8 g), and acetonitrile (70 ml) was stirred and refluxed for 16 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$), and then it was concentrated to afford9.5 g of a brown oil. The oil was taken up in ethyl acetate and ethereal HCl was added until the reaction was acidic. The crude, brown, hydrochloride salt ,was collected (8.4 g), and was immediately converted to the free base with NH_4OH, to afford 5.4 g of the compound as a brown oil. The oil was chromatographed on a Waters Preparative HPLC utilizing silica gel columns. Concentration of the appropriate fractions yielded 3.5 g of N-[5-acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide as a white solid, m.p.=108°–110° C.

ANALYSIS

Calculated for $C_{25}H_{28}FN_3O_4$: 66.21% C 6.22% H 9.27% N.

Found: 66.12% C 6.25% H 9.27% N.

EXAMPLE 68

3-[1-[3-(4-Ethyl-3-methoxyphenoxy)propyl]-4-piperidinyl]6-fluoro-1,2-benzisoxazole hydrochloride

(A) 4-ethyl-2-methoxyphenol

Acetovanillone (Aldrich, 11.0 g, 0.066 mol) was dissolved in absolute ethanol (200 ml) and added to 1.5 g of 5% palladium on carbon. A few drops of concentrated hydrochloric acid were added and the mixture hydrogenated on a shaker at 42 psi. The reaction mixture was filtered through celite, and the filtrate was concentrated to afford 10.3 g of a golden liquid. This was diluted with water, extracted with diethyl ether and the organic phase was washed with water and sodium bicarbonate. The solvent was dried ($MgSO_4$) and concentrated to afford 9.3 g of a slightly yellow liquid.

(B) 4-ethyl-2-methoxy-4-(3-chloropropoxy)benzene

A mixture of 4-ethyl-2-methoxyphenol (9.0 g, 0.059 mol), 3-chloro-1-bromopropane (13.0 g, 0.083 mol), K_2CO_3 (6.2 g) and acetone (200 ml) was stirred and refluxed for 16 hours. The reaction was allowed to cool, and then it was filtered. The filtrate was concentrated to a clear liquid. The liquid was diluted with dilute aqueous NaOH, and the basic mixture was extracted with diethyl ether. The diethyl ether was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford 11.9 g of a golden liquid. The liquid was flash

chromatographed. This gave a colorless liquid, 9.9 g of 4-ethyl-2-methoxy-4-(3-chloropropoxy)benzene.

(C)

3-[1-[3-(4-ethyl-2-methoxyphenoxy)propyl]-4-piperidinyl-6-fluoro-1,2-benzisoxazole hydrochloride

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.0 g, 0.018 mol), KI (0.4), K_2CO_3 (2.5), 4-ethyl-2-methoxy-4-(3-chloropropoxy)benzene (4.4 g, 0.018 mol) and acetonitrile was refluxed for 8 hours. The reaction was poured into water, and the aqueous suspension was extracted with ethyl acetate. The ethyl acetate extract was washed (water) dried ($MgSO_4$) and the solvent concentrated to afford 7.0 g of a brown oil. The oil was combined with 2.0 g from another sample, and the combined sample was flash chromatographed on silica gel. Concentration of the appropriate fractions yielded 4.4 g of a thick oil, which solidified on standing. The solid was dissolved in ethyl acetate and ethereal HCl was added to precipitate 4.5 g of a white hydrochloride salt. Recrystallization from acetone afforded 3.0 g (29%) of 3-[1-[3-(4-ethyl-2-methoxyphenoxy)propyl-]4-piperidinyl-6-fluoro-1,2-benzisoxazole hydrochloride as a white solid, m.p. = 150°–152° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_2O_3.HCl$: 64.21% C 6.74% H 6.24% N.

Found: 64.38% C 6.84% H 6.14% N.

EXAMPLE 69

1-[3,5-Dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone

(A) 3,5-dimethoxy-4-(3-bromopropoxy)acetophenone

To 3,5-dimethoxy-4-hydroxyacetophenone (5.2) in dimethylformamide (50 ml) at 0° C. under nitrogen, was added sodium hydride (700 mg, 1.1 eq, 98%). The resulting mixture was stirred for ten minutes until evolution of gas ceased. Potassium carbonate (4 g) was added, and then 1,3-dibromopropane was added. The mixture was heated at 60° C. for one hour. When the reaction was complete, the mixture was poured into a water/ice mixture and the resulting solution was extracted with ethyl acetate (600 ml). The ethyl acetate was washed with water, brine, and then concentrated to an oil (9 g). The product was purified by chromatography on silica gel to yield 3,5-dimethoxy-4-(3-bromopropoxy)acetophenone as a light oil, 7.6 g.

(B)

1-[3,5-dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 moles), K_2CO_3 (2.1 g, 15 mmoles), and 3,5-dimethoxy-4-(3-bromopropoxy)acetophenone (4.4 g, 13.8 moles) in acetonitrile (50 ml) was heated at reflux for 3 hr. At the end of the reaction, the mixture was diluted with dichloromethane (200 ml). The insolubles were filtered. The solution was concentrated to an oil (~10). The purification was done by flash chromatography on a silica gel column. The product was obtained as a colorless oil (3.85 g, 61%), which crystallized from ethanol (400 ml) to give 2.94 g of 1-[3,5-dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone as off-white crystals, m.p. = 107°–108° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_5$: 65.78% C 6.40% H 6.14% N.

Found: 65.84% C 6.44% H 6.15% N.

EXAMPLE 70

N-[3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide hemifumarate

(A) 3-(3-acetamidophenoxy)propyl bromide

To 3-acetamidophenol (15.1 g) in dichloromethane (500 ml, dry) was added potassium carbonate (20 g) and then 1,3-dibromopropane (30 g). The resulting mixture was heated at reflux for 6 hours and then overnight at room temperature. After an additional 24 hours, the reaction was complete. Solids were filtered from the reaction mixture, and the solution was concentrated to an oil, which was purified to yield 3-(3-acetamidophenoxy)propyl bromide, 13.2 g.

(B)

N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide hemifumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (9.25 g, 42 moles), K_2CO_3 (8 g, 58 moles) and 3-(3-acetamidophenoxy)propyl bromide (11.4 g, 42 mmoles) in acetonitrile (350 ml) was heated at reflux for 3 hours. At the end of the reaction, the reaction was cooled, filtered and the solids washed with dichloromethane (100 ml). The organic solvent was removed on a rotary evaporator to leave a crude oil ([18] 18 g). Purification was by flash chromatography on a silica gel column. The product thus purified was an oil, 12.2 g, 70%. Analytically pure sample was prepared by dissolving 3 g of free base in ethanol and treating with fumaric acid solution in ethanol (850 mg:5 ml). The N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide hemifumarate crystals obtained weighed 2.73 g, m.p. = 184°–186° C.

ANALYSIS

Calculated for $C_{23}H_{26}FN_3O_2.0.5C_4H_4O_4$: 63.95% C 6.01% H 8.94% N.

Found: 63.47% C 5.94% H 8.78% N.

EXAMPLE 71

3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline

A stirred mixture of N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxyl]phenyl]acetamide (9.2 g, 22 moles), prepared as described in the previous example, in 15% hydrochloric acid (110 ml) was heated at 100° C. for 2.5 hours until a homogeneous solution resulted. The reaction was cooled to 0° C. in an ice bath and basified with 50% NaOH. The product was extracted with ethyl acetate (3×200 ml). The ethyl acetate solution was washed with water, brine, then dried over Na_2SO_4. The solvent was removed. The crude product was purified on a flash chromatography column. The product thus obtained was a solid: 6.6 g (80%). Recrystallization from hot ethanol (50 ml) gave 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline as off-white crystals: 3.46 g, m.p. = 115°–117° C.

ANALYSIS

Calculated for $C_{21}H_{24}FN_3O_2$: 68.27% C 6.55% H 11.37% N.

Found: 68.34% C 6.53% H 11.31% N.

EXAMPLE 72

3-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyaniline

A mixture of 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenylacetamide (4.2 g, 9.5 mmoles), prepared as in Example 26 above, in 15% hydrochloric acid (60 ml) was heated at reflux (~110° C.) for 2 hours. At the end of the reaction, the solution was cooled to 0° C. then basified with 25% NaOH to pH of 10. The product was extracted into ethyl acetate (300 ml). The ethyl acetate solution was washed with water and brine, then dried over Na_2SO_4. The solvent was removed at reduced pressure. The crude oil was purified by flash chromatography on a silica gel column. The product thus purified was an oil, 2.6 g. Crystallization from ethanol (5 ml) and petroleum ether (3 ml) yielded 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyaniline as fine crystals: 1.2 g; m.p.=94°–95° C.

ANALYSIS

Calculated for $C_{22}H_{26}FN_3O_3$: 66.15% C 6.56% H 10.52% N.

Found: 66.16% C 6.54% H 10.44% N.

EXAMPLE 73

1-[4-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy-3-methylaminophenyl]ethanone fumarate

(A)

1-[(3-N-acetyl-N-methylamino)-4-hydroxyphenyl]ethanone

A solution of 2-methoxy(methylamino)benzene (26.0 g, 0.19 mol) and 1,2-dichloroethane was cooled to 10°–15° and a solution of acetyl chloride (33.8 g, 0.43 mol) dissolved in dichloroethane (50 ml) was dripped in slowly. Following this addition, an additional 100 ml dichloroethane was added. The reaction was cooled to 0° and aluminum chloride (72.3 g, 0.54 mol) was added over the course of 45 minutes so that the temperature did not exceed 10°. After complete addition, the reaction was heated to reflux and was stirred for 18 hours under nitrogen. The reaction was cooled and was poured into ice. The resulting aqueous phase was extracted further with dichloromethane and the combined extracts were washed with H_2O, dried with $MgSO_4$, and concentrated to yield 32.0 g of 1-[(3-N-acetyl-N-methylamino)-4-hydroxyphenyl]ethanone as a brown solid, m.p.=168°–171° C.

(B) 1-(4-hydroxy-3-methylaminophenyl]ethanone

A mixture of 1-((3-N-acetyl-N-methylamino)-4-hydroxyphenyl]ethanone (15.0 g, 0.0724 mol) and concentrated HCl (150 ml) was stirred at reflux for 3 hours. The heat was terminated and the reaction stood overnight. The reaction mixture was transferred to a 1 l beaker and was chilled in an ice-salt bath. Solid sodium bicarbonate was added cautiously until the pH was about 2, and the aqueous mixture was allowed to stand overnight. The reaction mixture was continued to be made basic by the addition of solid sodium bicarbonate. After pH 8 was achieved, the reaction mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with a 200 ml aliquot of water and this was then fed through a bed of celite. After washing the cake with fresh ethyl acetate the phases were separated. The ethyl acetate extract was washed several more times with water, dried with $MgSO_4$ and concentrated to yield 10.5 g of a dark solid of 1-(4-hydroxy-3-methylaminophenyl)ethanone.

(C)

1-[4-(3-chloropropoxy)-3-methylaminophenyl]ethanone

To a stirred suspension of sodium hydride (0.87 g, 0.0182 mol of a 50% oil dispersion) in dimethylformamide (25 ml) under nitrogen and cooled to 0° in an ice-salt bath was added, dropwise, a solution of 1-(4-hydroxy-3-methylaminophenyl)ethanone (3.0 g, 0.0182 mol) dissolved in dimethylformamide (55 ml) so that the temperature did not rise above 3°. After the addition was complete, the reaction was stirred for 80 minutes at ambient temperature. The reaction was cooled to 5° and a solution of 1-bromo-3-chloropropane (3.1 g, 0.0120 mol) in dimethylformamide (20 ml) was added dropwise. After this addition was complete, the ice bath was removed and the reaction was stirred at ambient temperature for 2.5 hours. Water (75 ml) was carefully added and after stirring vigorously for 5 minutes, the reaction was left to stand overnight. The aqueous mixture was extracted with ethyl acetate and the ethyl acetate extract was washed with water, dried with $MgSO_4$, and concentrated to yield 3.9 g of a dark solid. The compound was purified by preparative HPLC to afford 2.4 g of a beige solid. This was combined with an additional sample (3.8 g total) and two consecutive recrystallizations from ethanol gave 2.1 g (31%) of 1-[4-(3-chloropropoxy)-3-methylaminophenyl]ethanone as a fluffy, beige solid, m.p.=115°–117° C.

ANALYSIS

Calculated for $C_{12}H_{16}ClNO_2$: 59.63% C 6.67% H 5.79% N.

Found: 59.49% C 6.64% H 5.79% N.

(D)

1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy-3-methylaminophenyl]ethanone fumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (1.9 g, 0.079 mol), 1-[4-(3-chloropropoxy)-3methylaminophenyl]ethanone (1.9 g, 0.079 mol), K_2CO_3 (1.1 g), KI (0.1 g), and acetonitrile (95 ml) was refluxed for 16 hours. The reaction was poured into water and the aqueous suspension extracted with ethyl acetate. The extract was washed (water and brine), dried ($MgSO_4$), and then the solvent was concentrated to afford 3.2 g of a thick, brown oil. The oil was chromatographed on a Waters Prep 500 LC on silica gel columns, and concentration of the appropriate fractions afforded 1.5 g of a brown oil. The oil was dissolved in acetone and fumaric acid (0.4 g, 0.003 mol) was added, and 1.9 g of a white fumarate salt was collected. The salt was recrystallized from dimethylformamide to yield 1.1 g (25%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl] propoxy-3-methylaminophenyl]ethanone fumarate as a white solid, m.p.=198°–200° C.

ANALYSIS

Calculated for $C_{28}H_{32}FN_3O_6S$: 60.31% C 5.78% H 7.54% N.

Found: 60.02% C 5.88% H 7.68% N.

EXAMPLE 74

N-[3-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]acetamide

(A)

N-[3-(3-chloropropoxy)-4-methoxyphenyl]acetamide

To a stirred suspension, under nitrogen, of sodium hydride (1.8 g, 0.038 mol) in dimethylformamide (60 ml) was added dropwise, N-(3-hydroxy-4-methoxy)acetamide (6.1 g, 0.034 mol) dissolved in dimethylformamide (23 ml). After complete addition, the reaction was stirred at ambient temperature for 0.5 hour, and then 3-chloro-1-bromopropane (5.2 g, 0.033 mol) in dimethylformamide (10 ml) was added, dropwise. The reaction was stirred at ambient temperature for 16 hours, and then it was poured into water, and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$) and the solvent concentrated to afford a purple solid. The solid was triturated with diethyl ether and collected to afford 2.8 g of a purple solid. This sample was combined with a sample (1.2 g) from another run and was recrystallized from toluene twice to yield 2.9 g of an off-white solid. The solid was flash chromatographed on 200 g of silica gel, eluting the column with ethyl acetate, and subsequent concentration of the appropriate fractions afforded 2.4 g of a white solid. Recrystallization of the compound from toluene yielded 2.2 g (17%) of N-[3-(3-chloropropoxy-4-methoxyphenyl]acetamide, m.p.=112°–114° C.

ANALYSIS

Calculated for $C_{12}H_{16}ClNO_3$: 55.93% C 6.26% H 5.44% N.

Found: 56.25% C 6.29% H 5.44% N.

(B)

N-[3-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]acetamide

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (4.0 g, 0,017 mol), N-[3-(3-chloropropoxy)-4-methoxyphenyl]acetamide (4.3 g, 0.017 mol), K_2CO_3 (2.3 g), KI (0.2 g) and acetonitrile (200 ml) was refluxed for 10 hours. The cooled reaction mixture was filtered and the filtrate was concentrated to yield a dark oil. The oil was dissolved in acetone, and ethereal HCl was added to yield 5.7 g of a yellow hydrochloride salt. The salt was reversed to the free base and the resultant oil (5.2 g) was chromatographed on a Waters Associates Prep LC utilizing silica gel columns. Concentration of the appropriate fractions yielded 4.7 g of an oil, which was converted to a hydrochloride salt. The salt was converted to its free base yielding 2.8 g of a brown oil. The oil was stirred vigorously with ether to yield 1.4 g (18%) of N-[3-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-4-methoxyphenyl]acetamide as a white solid, 1.4 g, m.p.=109°–111° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_3S$: 63.00% C 6.17% H 9.18% N.

Found: 62.80% C 6.17% H 8.86% N.

EXAMPLE 75

1-[4-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrochloride

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (4.0 g, 0.017 mol), 1-[4-(3-chloropropoxy)-3-methoxyphenyl]ethanone (4.1 g, 0,017 mol), K_2CO_3 (2.3 g), KI (0.2 g), and acetonitrile (100 ml) was refluxed for 9 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The extract was washed (water), dried ($MgSO_4$), and the solvent was concentrated to afford 8.0 g of a brown oil. The oil was chromatographed on a Waters Prep 500 HPLC on silica gel columns. Concentration of the appropriate fractions afforded a gum-like residue, which upon trituration with isopropyl ether afforded 1.9 g of a white solid. The solid was dissolved in absolute ethanol, and ethereal HCl was added to precipitate 1.7 g of a hydrochloride salt. Concentration of the isopropyl ether filtrate, and similar treatment of the residue, afforded an additional 0.5 g of the salt. The samples were combined and recrystallized from absolute ethanol to yield 1.7 g (21%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrochloride as a white solid, m.p.=221°–223° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3S.HCl$: 60.18% C 5.89% H 5.85% N.

Found: 60.01% C 5.97% H 5.79% N.

EXAMPLE 76

N,N-Dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide

(A)

N,N-dimethyl-4-bromopropoxy-3-methoxybenzamide

To N,N-dimethyl-4-hydroxy-3-methoxybenzamide (5.64 g, 28.7 mmol) in acetonitrile (450 ml) was added potassium carbonate (7.9 g) followed by 1,3-dibromopropane (11.6 g). The resulting reaction mixture was refluxed for 3 hours and stirred at room temperature for 12 hours. The mixture was filtered and concentrated to an oil. Following purification by column chromatography, N,N-dimethyl-4-bromopropoxy-3-methoxybenzamide as a colorless oil (7.6 g) was obtained.

(B)

N,N-dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.9 g, 17.7 moles), N,N-dimethyl-4-bromopropoxy-3-methoxybenzamide (5.54 g, 17.5 mmoles) and K_2CO_3 (3 g) in acetonitrile (250 ml) was heated at reflux for one hour. At the end of the reaction, the insolubles were filtered and washed with dichloromethane. The solvent was removed on a rotary evaporator. The residue was purified by flash chromatography over a silica gel column. The product thus obtained as an oil weighed 7 . Crystallization from hot ethanol (45 ml) afforded analytically pure N,N-dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzamide, 3.95 g, 50%, as light yellow crystals, m.p.=126°–127° C.

ANALYSIS

Calculated for $C_{25}H_{30}FN_3O_4$: 65.92% C 6.64% H 9.22% N.

Found: 65.76% C 6.64% H 9.14% N.

EXAMPLE 77

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone oxime

A mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (4.3 g, 0.01 mol), prepared as in Example 3 above, hydroxylamine hydrochloride (1.3 g, 0.018 mol), ammonium acetate (1.7 g, 0.022 mol) and ethanol-H_2O was stirred and refluxed for 16 hours. The reaction was poured into water, and the mixture was cooled in an ice bath for 2 hours. The resultant, white solid was collected, washed with water and dried to yield 4.6 g of hydrochloride salt of the oxime, m.p. 216°–218° C. The compound was dispersed in water and ammonium hydroxide was added until the suspension was decidedly basic. The basic suspension was then extracted with dichloromethane, and after washing with water, drying ($MgSO_4$), and concentrating the extract, 3.0 g of white solid melting at 168°–170° C. were harvested. The compound was recrystallized from dimethylformamide to yield 2.3 g (52%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3methoxyphenyl]ethanone oxime as a white solid, m.p.=168°–170° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_4$: 65.29% C 6.39% H 9.52% N.

Found: 65.27% C 6.44% H 9.46% N.

EXAMPLE 78

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]methoxyphenyl]ethanone oxime O-methyl ether

A solution of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]methoxyphenyl]ethanone (4.3 g, 0.01 mol), prepared as in Example 3 above, methoxylamine hydrochloride (0.93 g, 0.01 mol) in pyridine (75 ml)/ethanol (75 ml) was refluxed for 16 hours. Most of the solvent was evaporated under reduced pressure, and the residue was diluted with water to precipitate 1.6 g of a white solid, m.p. 200°–201° C. The aqueous filtrate upon standing deposited another crop of white crystals, which yielded 1.2 g of a pale, yellow solid with a m.p. of 70°–72° C. The initial crop of crystals was converted to its free base with aqueous NaOH. After extractive workup with ethyl acetate, 1.2 g of the free base was obtained. The two samples were combined and recrystallized from isopropyl ether to afford 2.0 g (44%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]methoxyphenyl]ethanone oxime O-methyl ether as colorless crystals, m.p.=97°–99° C.

ANALYSIS

Calculated for $C_{25}H_{30}FN_3O_4$: 65.92% C 6.64% H 9.22% N.

Found: 65.89% C 6.86% H 9.15% N.

EXAMPLE 79

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrazone

A stirred mixture of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (4.3 g, 0.01 mol), prepared as in Example 3 above, hydrazine (0.8 g, 0.0025 mol), and ethanol (40 ml) was refluxed for 16 hours. The cooled solution was concentrated to yield an oily residue. The residue was triturated with water and the resultant solid was collected to afford 4.2 g of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone hydrazone as a yellow solid. The compound was recrystallized from isopropanol and then from toluene to afford 1.7 g (39%), m.p.=106°–108° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_4O_3$: 65.44% C 6.64% H 12.72% N.

Found: 65.38% C 6.55% H 12.55% N.

EXAMPLE 80

6-Fluoro]-3-[1-[3-[2-methoxy-4-(1-methylethenyl)-phenoxy]propyl]-4-piperidinyl]-1,2-benzisoxazole hydrochloride

A solution of butyllithium (4.7 ml of a 2.3M solution in hexanes, 0.0107 mol) in tetrahydrofuran (65 ml) was stirred under nitrogen and cooled to −70° in an isopropyl alcohol-dry ice bath. Methyltriphenylphosphonium bromide (3.8 g, 0.0106 mol) was added portionwise over the course of 10 minutes. After complete addition, the reaction was stirred at −65° for one hour and was then allowed to gradually warm up to ambient temperature, where it was stirred for an additional 3.5 hours. The reaction was cooled to 0°, and a solution of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone prepared as in Example 3 above (4.7 g, 0.0110 mol) dissolved in tetrahydrofuran (50 ml) was added, dropwise, over the course of 30 minutes. After the addition was complete, the reaction was stirred at ambient temperature for 19 hours. The reaction was poured into water and the aqueous mixture was extracted with diethyl ether. The diethyl ether extract was washed several times with water, dried with $MgSO_4$ and concentrated to yield 7.0 g of a light orange solid. Recrystallization from toluene-hexane provided 1.4 g of triphenylphosphine oxide and concentration of the filtrate afforded 5.5 g of a glassy, beige solid. This was combined with an additional sample (6.5 g total) and purification by preparative HPLC (Water's Associates prep LC/System 500) gave 5.2 g of a beige solid, which remained contaminated by triphenylphosphine oxide. The compound was taken up in anhydrous ethanol (300 ml) and methanol (5 drops) and ethereal HCl was added to precipitate 4.0 g of a pale, white solid, m.p.=192°–194° C.

ANALYSIS

Calculated for $C_{25}H_{30}ClFN_2O_3$: 65.14% C 6.56% H 6.08% N.

Found 64.95% C 6.62% H 6.04% N.

EXAMPLE 81

(E)-1-[4-[[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10 mmoles), K_2CO_3 (2 g), (E)-4-[(4-bromo-2-butenyl)oxy]-3-methoxyacetophenone (4.0 g, 1.3 eq) in acetonitrile (100 ml) was heated at reflux for 2 hours. At the end of the reaction, the solvent was removed on the rotary evaporator. The residue was extracted into dichloromethane (300 ml). The insolubles were filtered off. The dichloromethane was concentrated. The crude product was purified on a flash chromatography column. The product eluted as an oil, weight 2.87 g (64%). Recrystallization from ethanol:hexane (20 ml:5 ml) gave (E)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-

piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl]ethanone as off-white crystals: 2.46 g; m.p.=91°-93° C.

ANALYSIS

Calculated for $C_{25}H_{27}FN_2O_4$: 68.48% C 6.21% H 6.39% N.

Found: 68.28% C 6.12% H 6.27% N.

EXAMPLE 82

(Z)-1-[4-[(4-Chloro-2-butenyl)oxy]-3-methoxyphenyl]ethanone

A stirred mixture of 4-hydroxy-3-methoxyacetophenone (16.6 g, 0.1 mole), K_2CO_3 (14 g, 0.10 mole) and cis-1,4-dichloro-2-butene (Aldrich, 15 g, 0.12 mole) in acetonitrile (250 ml) was heated at reflux for 2.5 hr. The mixture was filtered and concentrated to an oil. Purification was by flash chromatography. The fractions containing the purest product were combined and concentrated to give white crystals, 7.7 g, 30% . This was recrystallized from ether to give analytical pure (Z)-1-[4-[(4-chloro-2-butenyl)oxy]-3-methoxyphenyl]ethanone (2.72 g), m.p.=64°-66° C.

ANALYSIS

Calculated for $C_{13}H_{15}ClO_3$: 61.30% C 5.94% H.

Found: 61.28% C 5.94% H.

EXAMPLE 83

(Z)-1-[4-[[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxyphenyl]ethanone

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.2 g, 10 mmoles), K_2CO_3 (1.8 g, 13 mmoles) and (Z)-1-[4-[(4-chloro-2-butenyl)oxy]-3-methoxyphenyl]ethanone (3.43 g, 9.7 mmoles) in acetonitrile (100 ml) was heated at reflux for 1½ hr. At the end of the reaction, the solvent was removed and the inorganics were filtered after addition of dichloromethane (250 ml). The dichloromethane solvent was removed again. The crude oil was purified on two flash chromatography columns to give a colorless oil (2.78 g). The oil was solidified by vigorously drying on a vacuum pump. Recrystallization from ethanol (10 ml) and hexane (2 ml) gave analytically pure (Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]3-methoxyphenyl]ethanone, 1.83 g, m.p.=57°-59° C.

ANALYSIS

Calculated for $C_{25}H_{27}FN_2O_4$: 68.48% C 6.21% H 6.39% N.

Found: 68.26% C 6.18% H 6.32% N.

EXAMPLE 84

(E)-1-[3-[[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperdinyl]-2-butenyl]oxy]-4-hydroxyphenyl]ethanone hydrochloride

The mixture of (E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4benzyloxyphenyl]ethanone (5.5 g, 10.7 mmole), acetic acid (50 ml), and hydrochloric acid (6 ml) was heated at 75° C. for 2 hr. At the end of reaction, the solvent was reduced about 20 ml on a rotary evaporator. The solution was poured into ice water (350 ml) and extracted with dichloromethane (3×250 ml). The dichloromethane solution was washed with brine and dried over Na_2SO_4. A solid formed on concentration of the solvent. This was collected by filtration (3.4 g). Recrystallization from hot methanol (40 ml) gave 1.82 g of (E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-hydroxyphenyl]ethanone hydrochloride as white crystals, 37.5% , m.p.=208°-210° C.

ANALYSIS

Calculated for $C_{24}H_{25}FN_2O_4.HCl$: 62.54% C 5.69% H 6.08% N.

Found: 62.40% C 5.60% H 6.04% N.

EXAMPLE 85

(E)-1-[3-[[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-benzyloxyphenyl]ethanone

(A) (E)-3-[(4'-bromo-2'-butenyl)oxy]-4-benzyloxyacetophenone

To 4-benzyloxy-3-hydroxyacetophenone (17.6 g) in acetonitrile (200 ml) was added potassium carbonate (10 g), followed by the addition of (E)-1,4-dibromobutene (19 g). The resulting mixture was heated at reflux for 3 hours. The mixture was concentrated, extracted into dichloromethane, and the potassium salt was removed by filtration. Solvent was removed, and the resulting material was purified by flash chromatography to yield 20.5 g of (E)-3-[(4'-bromo-2'-butenyl)oxy]-4-benzyloxyacetophenone as white crystals.

(E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-benzyloxyphenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5.62 g, 25.5 mmoles), K_2CO_3 (4 g, 29 mmoles), and (E)-3-[(4,-bromo-2'-butenyl)oxy]-4-benzyloxyacetophenone (10 g, 26.6 mmole) in acetonitrile (125 ml) was heated at reflux for 3.5 hr. The mixture was cooled and concentrated to a crude solid. The residue was extracted into dichloromethane (300 ml) and insolubles were filtered. The crude material from the dichloromethane solution was purified on a flash chromatography column. The product thus purified weighed 8 g as a pale white solid. Recrystallization from hot ethanol gave 7.11 g of (E)-1-[3-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4benzyloxyphenyl-]ethanone as off-white crystals, m.p.=124°-125° C.

ANALYSIS

Calculated for $C_{31}H_{31}FN_2O_4$: 72.36% C 6.07% H 5.44% N.

Found: 72.23% C 6.04% H 5.04% N.

EXAMPLE 86

6-Fluoro-3-[1-[3-[(5-methoxy-1H-indol-6-yl)oxy]-propyl]-4-piperidinyl]-1,2-benzisoxazole

(A) 6-(3-Chloropropoxy]-5-methoxyindole

To a stirred suspension of sodium hydride (0.94 g, 19.6 mmol of a 50% oil dispersion) in dimethylformamide (20 ml) under nitrogen and cooled to −5° was added, dropwise, 5-methoxy-6-hydroxyindole (3.2 g, 19.6 mmol) dissolved in dimethylformamide (60 ml) so that the temperature did not exceed −2°. After complete addition, the reaction was stirred for 45 minutes at 0°. While maintaining the reaction temperature between −5° and 0°, a solution of 1-bromo-3-chloropropane (3.1 g, 19.6 mmol) dissolved in dimethylformamide (15 ml) was slowly added. The mixture was stirred at ambient temperature under nitrogen for 21 hours. The reaction was cooled in an ice bath, and water was added to destroy the excess sodium hydride, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried with $MgSO_4$ and

concentrated to yield 5.3 g of a dark, oily liquid. This was combined with an additional sample, for a total of 10.0 g, and purification by preparative HPLC (Waters Associates prep LC/System 500) provided 5.1 g of a brown solid. A 2.5 g sample was recrystallized from isopropyl alcohol to yield 1.1 g (30%) of 6-(3-chloropropoxy)-5-methoxyindole as beige crystals, m.p.=73°-75° C.

ANALYSIS

Calculated for $C_{12}H_{14}ClNO_2$: 60.13% C 5.89% H 5.84% N.

Found: 60.26% C 5.86% H 5.77% N.

B.

6-Fluoro-3-[1-[3-[(5-methoxy-1H-indol-6-yl]oxy]-propyl]-4-piperidinyl]-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.5 g, 11.5 mmol), 6-(3-chloropropoxy)-5-methoxyindole (2.5 g, 10.4 mmol), K_2CO_3 (1.6 g, 11.5 mmol), KI (200 mg) and acetonitrile (100 ml) was stirred at reflux under nitrogen for 40 hours. The cooled reaction was poured into water and extracted with ethyl acetate. The ethyl acetate extract was washed with water, washed with brine, dried with $MgSO_4$ and concentrated to yield 4.0 g of a solid. The compound was recrystallized from ethanol to afford 3.3 g. Another recrystallization from ethanol (utilizing a charcoal treatment) provided 2.9 g (66%) of 6-fluoro-3-[1-[3-[(5-methoxy-1H-indol-6-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole as a beige solid, m.p.=156°-158° C.

ANALYSIS

Calculated for $C_{24}H_{26}FN_3O_3$: 68.07% C 6.19% H 9.92% N.

Found: 67.89% C 6.07% H 9.91% N.

EXAMPLE 87

6-Fluoro-3-[1-[3-[(1H-indol-7-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole hemifumarate

(A) 7-(3-Chloropropoxy)indole

To a stirred suspension of sodium hydride (0.8 g, 0.017 mol of a 50% oil dispersion) in dimethylformamide (20 ml), under nitrogen, was added dropwise 7-hydroxyindole (2.1 g, 0.0157 mol) in dimethylformamide (20 ml). After complete addition, the reaction was stirred at ambient temperature for 0.5 hour and then cooled to 15° C. To this cooled solution was added, dropwise, 1-bromo-3-chloropropane (2.5 g, 0.0157 mol) in dimethylformamide (5 ml). The reaction was then stirred at ambient temperature for 16 hours. The reaction was poured into water, and the aqueous suspension extracted with ethyl acetate. The ethyl acetate was washed with water, dried ($MgSO_4$), and the solvent was concentrated to afford a dark brown oil. Following flash chromatography on silica gel, 7-(3-chloropropoxy)indole was obtained as a colorless oil, 1.0 g.

ANALYSIS

Calculated for $C_{11}H_{12}ClNO$: 63.01% C 5.77% H 6.68% N.

Found: 63.25% C 5.61% H 6.65% N.

(B)

6-Fluoro-3-[1-[3-[(1H-indol-7-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole hemifumarate

A stirred mixture of 7-(3-chloropropoxy)-1H-indole (3.5 g, 0.017 mol), 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.5 g, 0.017 mol), K_2CO_3 (2.3 g) and acetonitrile (60 ml) was refluxed for 11 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed with water, dried ($MgSO_4$), and the solvent was concentrated to afford a dark oil. The oil was flash chromatographed on silica gel. Upon concentration of the appropriate fractions, 3.0 g of a white, foamy substance was obtained. The substance was dissolved in ethyl acetate (75 ml) and fumaric acid (0.97 g, 0.083 mol) was added. The mixture was briefly heated to reflux, and then stirred at ambient temperature for 1.5 hours. The resultant insoluble white fumarate salt was collected and afforded 4.2 g of product. Recrystallization of the salt from dimethylformamide yielded 3.1 g (36%) of 6-fluoro-3-[1-[3-[(1H-indol-7-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole hemifumarate as a white solid, m.p.=213°-215° C.

ANALYSIS

Calculated for $C_{25}H_{26}FN_3O_4$: 66.50% C 5.80% H 9.31% N.

Found: 66.23% C 6.14% H 9.39% N.

EXAMPLE 88

6-Fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (10.0 g, 0.045 mol), K_2CO_3 (10.0 g), 3-bromo-1-propanol (7.3 g, 0,046 mol) and acetonitrile (200 ml) was refluxed for 3 hours. The reaction was poured into H_2O and 7.1 g of a beige solid was collected. The filtrate was extracted with dichloromethane, and after concentration an additional 6.7 g of crude solid was harvested. The solids were combined and triturated with refluxing ethyl acetate to afford 8.0 g of 6-fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole as an off-white solid. A sample (4.0 g) was recrystallized from ethanol-water (with charcoal treatment) to yield 2.4 g (40%) of the alcohol as a white solid, m.p.=140°-142° C.

ANALYSIS

Calculated for $C_{15}H_{19}FN_2O_2$: 64.73% C 6.88% H 10.06% N.

Found: 64.79% C 6.97% H 10.03% N.

EXAMPLE 89

6-Fluoro-3-[1-(2-pyrimidinoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate

To a stirred suspension of 6-fluoro-3-[1-(3-hydroxypropyl)-4-piperidinyl]-1,2-benzisoxazole (3.6 g, 0.013 mol) in tetrahydrofuran (50 ml) was added dropwise, potassium bistrimethylsilylamide (2.6 g, 0.013 mol) dissolved in tetrahydrofuran (20 ml). After complete addition, the reaction was stirred at ambient temperature for 5 min, and then 2-chloropyrimidine (1.6 g, 0.014 mol) was added. The reaction was stirred at ambient temperature for 4 hours, and TLC at this time indicated an incomplete reaction. An additional quantity of the base (0.5 g) was added, and the reaction was allowed to proceed at ambient temperature for 14 additional hours. The reaction was poured into water and the aqueous mixture was extracted with dichloromethane. The extract was washed (H_2O), dried (K_2CO_3), and the solvent was concentrated to afford a wet solid. The solid was triturated with diethyl ether and the product that separated was collected to yield 1.0 g of the starting alcohol. The filtrate was then concentrated to afford 3.8 g of a waxy, yellow solid. This material was combined with 2.6 g from another run and the combined sample

flash chromatographed on silica gel, eluting first with ethyl acetate and then with 8% diethylamine-ethyl acetate. Concentration of the appropriate fractions afforded 3.0 g of the desired compound as a yellow solid. The solid was converted to a fumarate salt with fumaric acid in acetone, and then reversed to its free base. It was combined with another sample and the combined sample (3.8 g) chromatographed on silica gel on HPLC (4.5% methanoldichloromethane as eluent). Concentration of the appropriate fractions yielded 1.6 g of a yellow solid. A fumarate salt was prepared to yield 2.1 g (16%) of 6-fluoro-3-[1-[(2-pyrimidinoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate, m.p.=184°–186° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_4O_6$: 58.47% C 5.33% H 11.86% N.

Found: 58.52% C 5.34% H 11.80% N.

EXAMPLE 90

6-Aceto-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan

(A) 6-aceto-2-mesyloxymethyl-1,4-benzodioxan

6-Aceto-2-hydroxyethyl-1,4-benzodioxan (3.39 g, 16.3 mmol) was dissolved in trichloromethane (100 ml). Triethylamine (2.5 g) was added to mesylchloride (2.5 g, 1.35 eq) at 0° C. The mixture was stirred for 2 hours at room temperature. The mixture was then diluted, washed with an ice/dilute hydrochloric acid mixture (150 ml), washed with sodium bicarbonate and brine, dried over magnesium sulfate, and concentrated to yield 5.6. Following chromatography on a SiO_2 column, 3.64 g (78% yield) of 6-aceto-2-mesyloxymethyl-1,4-benzodioxan were obtained.

(B)

6-aceto-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 mmoles), K_2CO_3 (2 g, 14.5 mmoles) and 6-aceto-2-mesyloxymethyl-1,4-benzodioxan (3.5 g, 12 mmoles) in acetonitrile (100 ml) was heated at reflux for 3 hr. At the end of the reaction the solvent was removed on a rotary evaporator. The residue was extracted into dichloromethane (350 ml) and the insolubles were filtered off. The dichloromethane solution was concentrated and the crude oil was purified by flash chromatography. The product thus obtained weighed 3.38 g (59%). Recrystallization from ethanol gave 6-aceto-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan as light yellow crystals (3.2 g), m.p.=122°–123° C.

ANALYSIS

Calculated for $C_{23}H_{23}FN_2O_4$: 67.31% C 5.65% H 6.83% N.

Found: 67.24% C 5.50% H 6.75% N.

EXAMPLE 91

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-methyl-1,4-benzodioxan

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 13.6 mmoles), K_2CO_3 (2.45 g, 17.7 mmoles), 2-methanesulfonyloxymethyl-1,4-benzodioxan (3.35 g, 13.7 mmole) in acetonitrile (100 ml) was heated at reflux for 12 hours. At the end of the reaction, the insolubles were filtered and rinsed with dichloromethane. The organic solution was concentrated. The crude oil was purified by flash chromatography on a silica gel column. The fractions containing the pure product were pooled and concentrated to a light yellow oil (3.94: g, 74%). Crystallization from ethanol and petroleum ether gave 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]methyl-1,4-benzodioxan as off-white crystals, 2.22 g, m.p.=86°–87° C.

ANALYSIS

Calculated for $C_{21}H_{21}FN_2O_3$: 68.47% C 5.75% H 7.60% N.

Found: 68.33% C 5.75% H 7.51% N.

EXAMPLE 92

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,4-benzodioxan

(A) 2-mesyloxyethyl-1,4-benzodioxan

To the compound 2-hydroxyethyl-1,4-benzodioxan (11.96 g) in dichloromethane (450 ml) was added triethylamine (0.12 mol, 10 ml). Mesylchloride (9.2 g) was then added dropwise and the reaction mixture was stirred for one hour at room temperature. After completion of the reaction, the solution was washed with water, brine, and concentrated to an oil, which was purified by chromatography on silica gel to yield 2-mesyloxyethyl-1,4-benzodioxan, 17.08 g.

(B)

2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,4-benzodioxan

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (4.7 g, 21 moles), K_2CO_3 (3.5 g, 25.4 moles) and 2-mesyloxyethyl-1,4-benzodioxan (5.5 g, 21.3 mmoles) in acetonitrile (250 ml) was heated at reflux for 3.5 hours. At the end of the reaction, insolubles were filtered. The solid was washed with dichloromethane (200 ml). The solutions were combined and evaporated to an oil. This crude oil was purified by flash chromatography on a silica gel column. The material thus obtained was crystallized from ethanol. The 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,4-benzodioxan crystals were collected and weighed 3.8 g, 48%, m.p.=112°–113° C.

ANALYSIS

Calculated for $C_{22}H_{23}FN_2O_3$: 69.09% C 6.06% H 7.32% N.

Found: 69.17% C 6.02% H 7.31% N.

EXAMPLE 93

6-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-7-methoxy-1-tetralone

(A) 6-(3-chloropropoxy)-1-tetralone

A mixture of 6-hydroxy-7-methoxy-1-tetralone (J. Org. Chem., 1985, 50, 4937) (1.5 g, 7.8 mmol), K_2CO_3 (1.7 g, 12.3 mmol), and acetone (30 ml) was stirred at reflux under nitrogen for 45 minutes. The reaction was cooled to ambient temperature and a solution of 1-bromo-3-chloropropane (1.9 g, 12.1 mmol) dissolved in 8 ml acetone was dripped into the mixture. After total addition, the reaction was heated to reflux and stirred under nitrogen for 21 hours. The reaction was cooled to ambient temperature and filtered. The filter cake was washed well with acetone and the filtrate was concentrated to yield 2.0 g 6-(3-chloropropoxy)-7-methoxy-1-tetralone as an amber oil.

(B)
6-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-7-methoxy-1-tetralone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (0.78 g, 3.6 mmol), K_2CO_3 (0.60 g, 4.1 mmol), KI (100 mg), 6-(3-chloropropoxy)-7-methoxy-1-tetralone (0.87 g, 3.2 mmol), and acetonitrile (50 ml) was stirred at reflux under nitrogen for 17 hours. The cooled reaction was poured into 100 ml of water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried with $MgSO_4$ and concentrated to yield 1.7 g of a brown oil. The oil was purified by preparative HPLC (Waters Associates Prep LC/system 500) to afford 1.0 of a light brown solid. This was combined with an additional sample (2.3 g total) and recrystallization from ethanol yielded 1.7 g. A subsequent recrystallization from ethanol gave 1.25 g (36%) of 6-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-7-methoxy-1-tetralone as a beige powder, m.p.=129°-131° C.

ANALYSIS

Calculated for $C_{26}H_{29}FN_2O_4$: 69.01% C 6.46% H 6.19% N.

Found: 68.77% C 6.43% H 6.16% N.

EXAMPLE 94

N-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propyl]-6-acetyl-2-benzoxazolinone

(A) N-(3-chloropropyl)-2-benzoxazolinone

To a stirred suspension of sodium hydride (7.8 g, 0.16 mol, ether-washed) in dimethylformamide (75 ml) was added dropwise under nitrogen, 2-benzoxazolinone (20.0 g, 0.15 mol) dissolved in dimethylformamide (150 ml). After complete addition the reaction was stirred at ambient temperature for 30 min, and then it was cooled to −5° C. with an ice-acetone bath. A solution of 3-chloro-1-bromopropane (46.6 g, 0.30 mol) in dimethylformamide (50 ml) was added dropwise (temperature never exceeded 0° C.). The reaction was allowed to reach ambient temperature and was stirred for 16 hours. The reaction was poured into water, and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate was washed with water, dried ($MgSO_4$), and the extract concentrated to afford 21.9 of a brown solid. The solid was recrystallized from toluene-hexane to afford N-(3-chloropropyl)-2-benzoxazolinone as large needles, 15.6 g, m.p.=264°-266° C.

(B) N-(3-chloropropyl)-6-acetyl-2-benzoxazolinone

A mixture of N-(3-chloropropyl)-2-benzoxazolinone (8.5 g, 0.04 mol), polyphosphoric acid (100 g), and acetic acid (2.4 g, 2.3 ml, 0.04 mol), was stirred and heated at 100° C. for 2 hours. The hot solution was poured into ice-water to deposit a yellow gum. The mixture was extracted with dichloromethane, and insolubles were filtered. The dichloromethane extract was washed with water, dried (K_2CO_3), and concentrated to afford 6.4 g of a slightly green solid. This was recrystallized from ethanol (95%) to yield N-(3-chloropropyl)-6-acetyl-2-benzoxazolinone as a brown solid, 3.5 g, m.p.=100°-103° C.

(C)
N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propyl]-6-acetyl-2-benzoxazolinone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.0 g, 0.009 mol), N-(3-chloropropyl)-6-acetyl-2-benzoxazolinone (2.4 g, 0.009 mol), K_2CO_3 (3.6 g), a few crystals of KI, and acetonitrile (50 ml) was stirred and refluxed for 13 hours. The reaction was poured into water, and a dark, brown solid that separated was collected to afford 3.3 g of crude product. The solid was chromatographed on a Waters Prep 500 HPLC. Concentration of appropriate fractions afforded 2.3 g of a yellow solid, and recrystallization from ethyl acetate yielded 1.2 g (31%) of N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]-6-acetyl-2-benzoxazolinone, m.p.=152°-154° C.

ANALYSIS

Calculated for $C_{24}H_{24}FN_3O_4$: 65.89% C 5.53% H 9.61% N.

Found: 65.67% C 5.48% H 9.52% N.

EXAMPLE 95

N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propyl]phthalimide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (6.44 g, 29.1 mmole), K_2CO_3 (6.4 g, 46 mmoles), N-(3-bromopropyl)phthalimide (8.4 g, 31 mmoles) in acetonitrile (150 ml) was heated at reflux for 3.5 hr. The insolubles were filtered. The solvent was removed at reduced pressure and the residue was purified by silica gel column chromatography to give N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]phthalimide as a white solid. Recrystallization from ethanol yielded 9.8 g (83%) of off-white crystals, m.p.=129°-1300C.

ANALYSIS

Calculated for $C_{23}H_{22}FN_3O_3$: 67.89% C 5.44% H 10.31% N.

Found: 67.49% C 5.38% H 10.13% N.

EXAMPLE 96

1-(3-Aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)-piperidine dihydrochloride

A mixture of N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]phthalimide (8.5 g, 21 moles), hydrazine monohydrate (1.5 g, 30 mmoles) in methanol (60 ml) was heated at reflux for 2 hours. At the end of the reaction, methanol was removed to leave a crude solid. To this was added water (60 ml), then the mixture was acidified with HCl to pH 1. The insolubles were filtered with the aid of a pad of celite. The aqueous solution was basified with 50% NaOH, (pH 13), then extracted with dichloromethane. The combined dichloromethane solution was washed with brine, then dried to a colorless oil (4.5 g). The analytical sample (1.5 g) was prepared by treating the oil with HCl in ethanol at 0° C. The 1-(3-aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride was obtained as white crystals, 2.03 g, m.p.=231°-234° C.

ANALYSIS

Calculated for $C_{15}H_{20}FN_3O.2HCl$: 51.44% C 6.33% H 12.00% N.

Found: 51.35% C 6.49% H 11.90% N.

EXAMPLE 97

cis-2-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]-hexahydro-1H-isoindole-1,3-dione hydrochloride

A mixture of 1-(3-aminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (3.01 g, 10.8 moles) and cis-1,2-cyclohexane-dicarboxylic anhydride (1.9 g, 12.3 mmoles) in dry pyridine (30 ml) was heated at reflux for

16 hours. The dark brown solution was concentrated to dryness on a rotary evaporator. The crude residue was purified twice by flash chromatography over a silica gel column. The pure product thus obtained weighed 2.5 g (67%). This was converted to the hydrochloride salt by treatment with HCl in ethanol (50 ml). The cis-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]-hexahydro-1H-isoindole-1,3-dione hydrochloride crystals so obtained weighed 3.0 g, m.p.=242°–245° C.

ANALYSIS

Calculated for $C_{23}H_{28}FN_3O_3$.HCl: 61.14% C 6.50% H 9.34% N.

Found: 61.32% C 6.32% H 9.27% N.

EXAMPLE 98

N-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-butyl]phthalimide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5.5 g, 25 mole), 4-bromobutylphthalimide (8.0 g, 28.3 moles, 1.13 eq), K_2CO_3 (4.55 g, 32 mmoles) in acetonitrile (100 ml) was heated at reflux for 3 hr. At the end of the reaction, the mixture was filtered. The insolubles were washed with dichloromethane (200 ml). The organic solution was concentrated gradually to allow crystallization. The crude crystals (5.9 g) were collected. The mother liquor was concentrated to a solid (5.5 g). Purification was by flash chromatography over a silica gel column. The product (3.8 g) thus purified was recrystallized from ethanol (70 ml) to give 2.48 g of N-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-butyl]phthalimide as white crystals, m.p.=144°–146° C.

ANALYSIS

Calculated for $C_{24}H_{24}FN_3O_3$: 68.39% C 5.74% H 9.97% N.

Found: 68.34% C 5.74% H 9.84% N.

EXAMPLE 99

1-(4-Aminobutyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl]piperidine dihydrochloride

A mixture of N-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl) piperidinyl]butyl]phthalimide (6.9 g, 16.4 mmoles) and hydrazine monohydrate <1.64 g, 32.8 mmoles) in methanol (70 ml) was heated at reflux for 3 hours. At the end of the reaction, methanol was removed to leave a crude solid. This was dissolved in water and acidified with HCl to pH 2. The insolubles were filtered. The aqueous solution was basified with 50% NaOH, and then extracted with dichloromethane. The dichloromethane solution was washed with water and brine, and then dried over $MgSO_4$. The solvent was removed to a colorless oil: 4.48 . This oil was treated with 2.5 equivalents of HCl in ethanol. The solid was collected. Recrystallization from ethanol (65 ml) and methanol (20 ml) gave 2.0 of 1-(4-aminobutyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine dihydrochloride as white crystals, m.p.=234°–237° C.

ANALYSIS

Calculated for $C_{16}H_{22}FN_3O.2HCl$: 52.75% C 6.64% H 11.53% N.

Found: 52.37% C 6.59% H 11.07% N.

EXAMPLE 100

cis-2-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl]-hexahydro-1H-isoindole-1,3-dione hydrochloride

A mixture of 1-(4-aminobutyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (4.7 g, 16.1 mmoles) and cis-1,2-cyclohexanedicarboxylic anhydride (3.23 g, 21 mmoles) in pyridine (45 ml) was heated at reflux for 8 hours. At the end of the reaction, pyridine was removed to dryness. The crude product was purified on a silica gel column. The material thus obtained weighed 3.18 g (45%) as a clear oil. This oil was dissolved in ethanol (15 ml), then was treated with HCl in ethanol (45 ml). Crystallization took place upon cooling. The crystals were collected, 3.2 g, m.p.=229°–231° C.

ANALYSIS

Calculated for $C_{24}H_{30}FN_3O_3$.HCl: 62.13% C 6.73% H 9.06% N.

Found: 61.79% C 6.68% H 8.92% N.

EXAMPLE 101

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]thio]-3-methoxyphenyl]ethanone

(A)

1-[4-[(3-chloropropyl)thio]-3-methoxyphenyl]ethanone

A mixture of 1-(4-thio-3-methoxyphenyl)ethanone (10.0 g, 0.0549 mol), potassium carbonate (9.0 g, 0.0651 mol), and acetone (100 ml) was stirred at reflux under nitrogen for 30 minutes. The reaction was cooled to ambient temperature and a solution of 1-bromo-3-chloropropane (6.5 ml, 9.5 g, 0.0604 mol) dissolved in acetone (25 ml) was dripped into the reaction. After complete addition, the reaction was heated to reflux and stirred under nitrogen for 17 hours. After the reaction was carried to substantial completion, the reaction mixture was filtered and the resulting filter cake was washed with acetone. The filtrate was concentrated to provide an amber oil. A small sample was solidified by trituration with hot cyclohexane to provide 1-[4-[(3-chloropropyl)thio]-3-methoxyphenyl]ethanone as a yellow solid, 11.7 g, m.p. 53°–55° C.

(B)

1-[4-[[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]thio]-3-methoxyphenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazol (3.0 g, 0.0136 mol), 1-[4-[(3-chloropropyl)thio]-3-methoxyphenyl]ethanone (3.5 g, 0.0136 mol), K_2CO_3 (2.3 g, 0.0166 mol), KI (200 mg) and CH_3CN (100 ml) was stirred at reflux under nitrogen for 7.5 hours and then was left at ambient temperature for 65 hours. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate extract was washed twice with water, once with brine and dried over $MgSO_4$. The solvent was removed in vacuo to afford 6.8 g of a light brown oil. The sample was purified by flash chromatography. Concentration of appropriate fractions yielded 3.0 g. Recrystallization from ethanol provided 2.4 g (41%) of 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl]thio]-3-methoxyphenyl]ethanone as a beige solid, m.p.=93°–95° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_3S$: 65.14% C 6.15% H 6.33% N.

Found: 64.66% C 6.17% H 6.26% N.

EXAMPLE 102

4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-[4-(2'-methxoyphenyl)]butylpiperidine maleate

(A) 2-(4-bromobutyl]anisole

2-Bromoanisole (2.0 g, 1.07 mmol) in tetrahydrofuran (20 ml) was cooled to −78° C. under nitrogen and secondary butyllithium (1.3M, 10 ml, 1.3 eq) was charged into the resulting solution for two hours. The solution was quenched with 1,4-dibromobutane (3.2 g) and allowed to stir at ambient temperature overnight. The mixture was diluted with ethyl acetate, washed with water and brine, and concentrated to an oil. Following chromatography on a SiO_2 column, 2.4 g of 2-(4-bromobutyl)anisole were obtained.

(B)

4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2-methoxyphenyl]butylpiperidine maleate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.36 g, 10.7 mole), K_2CO_3 (2 g, 14.5 mmoles) and 2-(4-bromobutyl)anisole (2.4 g, 10 moles) in acetonitrile (100 ml) was heated at reflux for 2.5 hr. At the end of reaction, the solvent was removed. The residue was extracted into dichloromethane (200 ml) and filtered. The dichloromethane solution was concentrated. The crude oil obtained was purified on a flash chromatography column. The material thus purified was a light yellow oil (2.73 g, 53%). This oil was dissolved in ethanol and treated with maleic acid (607 mg, 1.0 eq) in ethanol. The 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2'-methoxyphenyl)butylpiperidine maleate crystals formed on concentration and subsequent cooling to 0° C. These were collected and dried to yield 2.05 g, m.p.=132°–133° C.

ANALYSIS

Calculated for $C_{23}H_{27}FN_2O_2.C_4H_4O_4$: 65.05% C 6.27% H 5.62% N.

Found: 65.25% C 6.30% H 5.70% N.

EXAMPLE 103

1-[4-[4-[1-(1,3-Dithian-2-yl)ethyl]phenyl]butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine

(A) 4-bromo-1-[1,3-dithian-2-yl)ethylbenzene

To the compound p-bromoacetophenone (36.85 g, 0.185 mol) in trichloromethane (300 ml) was added 1,3-propanedithiol (25 g, 0.23 mol) and boron trifluoride etherate (3 ml). The resulting mixture was stirred at room temperature for 48 hours. The mixture was diluted with dichloromethane (500 ml), washed twice with 10% sodium hydroxide (200 ml), water, and brine, and then dried (Na_2SO_4). The product was concentrated to an oil. A portion was stirred with ether (100 ml) and a crystalline product was formed. The crystalline product was recovered by filtration and purified by recrystallization to yield 4-bromo-1-(1,3-dithian-2-yl)ethylbenzene.

(B) 4-(4-bromobutyl]-1-[1,3-dithian-2-yl)ethylbenzene

A solution of 4-bromo-1-(1,3-dithian-2-yl)ethylbenzene (27.2 g, 94 moles) in tetrahydrofuran (200 ml) was charged with sec-butyllithium (99 ml, 1.3M in cyclohexane, 0.13 mole) dropwise at −78° C. under nitrogen. The mixture was stirred at ambient temperature for 1.5 hours, and then quenched with 1,4-dibromobutane (42 g, 0.2 mole). After being stirred for 3 hours, the mixture was poured into ethyl acetate, and then washed with water and brine. The organic solution was then dried (Na_2SO_4) and concentrated to an oil. The crude product was purified by flash chromatography over silica gel column. The 4-(4-bromobutyl)-1-(1,3-dithian-2-yl)ethylbenzene thus purified was a light oil, 22.3 g.

ANALYSIS

Calculated for $C_{15}H_{21}BrS_2$: 52.17% C 6.13% H.

Found: 52.60% C 6.25% H.

(C)

1-[4-(1,3-dithian-2-yl)ethyl]phenyl-4-(6-fluoro-1,2-benzisoxazol-3-yl]butylpiperidine

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5.4 g, 24.5 mmoles), K_2CO_3 (4.2 g, 30 mmoles), 4-(4-bromobutyl)-1-(1,3-dithian-2-yl)ethylbenzene (8.5 g, 24.6 mmoles) in acetonitrile (200 ml) was heated at reflux for 2.5 hours. At the end of the reaction, the mixture was filtered and the solvent was concentrated. The crude (13 g) was purified by flash chromatography over a silica gel column. The material thus purified (8.67 g; 72%) was recrystallized from ethanol (50 ml) and hexane (100 ml) to afford 6.6 g of 1-[4-(1,3-dithian-2-yl)ethyl]phenyl-4-(6-fluoro-1,2-benzisoxazol-3-yl)butylpiperidine as light yellow crystals, m.p.=108°–110° C.

ANALYSIS

Calculated for: 66.91% C 6.86% H 5.78% N.

Found: 66.72% C 6.76% H 5.71% N.

EXAMPLE 104

1-[4-(4'-Acetophenyl)butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine

A solution of 1-[4-(1,3-dithian-2-yl)ethylphenyl]butyl-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (5.6 g, 11.6 mmoles), water (5 ml), and methanol (30 ml), in acetone (50 ml), was treated with mercury (II) perchlorate trihydrate (5 g, 1.1 eq.) at room temperature. After 30 minutes, the reaction was completed. The solids were filtered, and the solvent was removed on a rotary evaporator. The crude product was dissolved in ethyl acetate (500 ml) and washed with water, brine, then dried over Na2SO4. The solvent was removed to give a crude oil. The purification was by flash chromatography over a silica gel column. The oil thus obtained (2.67 g, 50%) was combined with 1.1 g of oil prepared in the same fashion. Crystallization from ethanol (10 ml) and hexane (20 ml) yielded 1-[4-(4'-acetophenyl)butyl]-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine as off-white crystals, 2.32 g, m.p.=85°–86° C.

ANALYSIS

Calculated for $C_{24}H_{27}FN_2O_2$: 73.07% C 6.90% H 7.10% N.

Found: 72.68% C 7.05% H 7.09% N.

EXAMPLE 105

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3-methoxyphenyl]ethanone

To a stirred suspension of sodium hydride (0.37 g, 0.007 mol of a 50% oil dispersion) in dimethylformamide (20 ml) was added, dropwise, 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3hydroxyphenyl]ethanone (2.9 g, 0.007 mol) dissolved in dimethylformamide (25 ml). The reaction was stirred at ambient temperature for 15 minutes, and then it was cooled with an ice bath to about 5° C., whereupon methyl iodide (1.0 g, 0.007 mol) in dimethylformamide (1 ml) was added dropwise. The reaction was stirred at

ambient temperature for 30 min, and then water was added. The resulting aqueous mixture was extracted with ethyl acetate, the extract washed with water, dried ($MgSO_4$), and the solvent was concentrated to afford 4.9 g of a brown oil, which solidified on standing. The solid was flash chromatographed on silica gel. The appropriate fractions were concentrated to yield 2.7 g of product as a yellow solid. Recrystallization from toluene-hexane yielded 2.0 g (67%) of analytically pure 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3-methoxyphenyl]ethanone as a yellow solid, m.p.=96°-98° C.

ANALYSIS

Calculated for $C_{24}H_{28}FN_3O_3$: 67.75% C 6.63% H 9.88% N.

Found: 67.93% C 6.72% H 9.80% N.

EXAMPLE 106

(2,4-Difluorophenyl)-[1-(phenylmethyl)-3-pyrrolidinyl]methanone oxalate

In a 1 l round bottom flask, a solution of ethyl-N-benzyl-3-pyrrolidine carboxylate (21.8 g, 11.7 mmoles) in 140 ml of 6N HCl was heated at reflux for 2.5 hours. The solution was cooled and the solvent was removed to dryness with a vacuum pump. The residue was then treated with thionyl chloride (100 ml) for 16 hours at room temperature. After the reaction, the excess thionyl chloride was vacuum stripped to dryness (60° C., 4 hrs). To the residue in the flask was added 1,3-difluorobenzene (30 g, 26 mmoles) followed by aluminum chloride (25 g, 18.7 mmoles) in portions at room temperature. When the mixture turned homogeneous (in about 10 minutes) it was then heated at 55° C. for 1 hour. After the reaction was complete, excess 1,3-difluorobenzene was removed under reduced pressure. The residue was partitioned between ice/water and dichloromethane (700 ml) and basified with 50% NaOH solution to pH 10. The dichloromethane solution was washed with water and brine, then dried over anhydrous $MgSO_4$. The solvent was stripped and the crude oil (31 g) was purified by flash chromatography over a silica gel column. The pure product thus obtained weighed 26 g (74%) as a yellow oil. An analytical sample was prepared by dissolving 4.2 of the oil in ethanol and treating with an ethanol solution of oxalic acid (1.33 g, 14.8 mmoles). To the mixture was added ether dropwise to cause crystallization. Recrystallization from ethanol and ether gave 2.63 g of (2,4-difluorophenyl)[1-(phenylmethyl)-3-pyrrolidinyl]methanone oxalate as white crystals, m.p.=114°-116° C.

ANALYSIS

Calculated for $C_{20}H_{19}FNO_5$: 61.38% C 4.89% H 3.58% N.

Found: 61.16% C 4.80% H 3.60% N.

EXAMPLE 107

6-Fluoro-3-[1-phenylmethyl)-3-pyrrolidinyl]-1,2-benzisoxazole fumarate

(A)

(2,4-difluorophenyl)[1-(phenylmethyl)-3-pyrrolidinyl]-methanone oxime

To the compound (2,4-difluorophenyl)[1-(phenylmethyl)-3-pyrrolidinyl]methanone (22 g) in 95% ethanol (350 ml) and water (100 ml) was added $NH_2OH.HCl$ (10.1 g) and ammonium acetate (12.7 g, 2.1 eq). The resulting mixture was refluxed for 3.5 hours. The mixture was then allowed to stir at room temperature for 24 hours. The reaction mixture was concentrated to remove ethanol, poured into water (500 ml), and extracted with dichloromethane (500 ml). This was followed by washing with water, brine, and drying over magnesium sulfate. The product was concentrated to an oil and purified by column chromatography to yield 12 g of (2,4-difluorophenyl)[1-(phenylmethyl)-3-pyrrolidinyl]methanone oxime.

(B)

6-fluoro-3-[1-(phenylmethyl)-3-pyrrolidinyl]-1,2-benzisoxazole fumarate

A mixture of (2,4-difluorophenyl)[1-(phenylmethyl-3-pyrrolidinyl]methanone oxime (10.8 g, 34.2 mmoles), potassium hydroxide (10 g), water (100 ml), and ethanol (100 ml) was heated at reflux for 2 hr. At the end of the reaction, the solution was cooled and ethanol was removed on a rotary evaporator. The aqueous mixture was diluted with water (100 ml) then extracted with dichloromethane (500 ml). The organic solution was washed with brine and dried over anhydrous $MgSO_4$. The solution was concentrated to an oil (9.8 g). The crude product was purified by flash chromatography over a silica gel column. The product thus obtained weighed 4.46 g (44%) as a light yellow oil. The oily product was dissolved in ethanol, and then treated with a solution of fumaric acid (1.73 g, 1.0 eq) in ethanol. Crystallization took place slowly with the addition of isopropyl ether. Recrystallization from ethanol (15 ml) gave 4.6 g of 6-fluoro-3-[1-(phenylmethyl)-3-pyrrolidinyl]-1,2-benzisoxazole fumarate as white crystals, m.p.=142°-144° C.

ANALYSIS

Calculated for $C_{22}H_{21}FN_2O_5$: 64.07% C 5.13% H 6.81% N.

Found: 64.11% C 5.05% H 6.89% N.

EXAMPLE 108

(E)-1-[4-[(4-bromo-2-butenyl)oxy]-3-methoxyphenyl-]ethanone

A mixture of 4-hydroxy-3-methoxyacetophenone (10 g, 59 moles), K_2CO_3 (10 g, 1.2 q) and 1,4-dibromo-2-butene (>95% trans, Aldrich, 18 g, 1.2 eq) in acetone (500 ml) was heated at 55° C. for 3 hr. At the end of the reaction, the solvent was concentrated. The crude product was extracted into dichloromethane (750 ml) and the insolubles were filtered; then the solution was concentrated again to an oil. Purification on a silica gel column (SiO_2, 100 g, eluted with dichloromethane) yielded 7.25 g (40%) of white solid. Recrystallization from ether gave analytically pure (E)-1-[4-[(4-bromo-2-butenyl)oxy]-3-methoxyphenyl]ethanone (3.91 g), m.p.=71°-72° C.

ANALYSIS

Calculated for $C_{13}H_{15}BrO_3$: 52.19% C 5.50% H.

Found: 52.12% C 4.94% H.

EXAMPLE 109

4-(3-Chloropropoxy)-3-methoxybenzaldehyde

A mixture of vanillin (30.4 g, 0.2 mol), K_2CO_3 (27.6 g) and acetone (150 ml) was stirred and refluxed for 0.5 hours. Heating was removed and 1-bromo-3-chloropropane (40.8 g, 0.26 mol) in acetone was added dropwise. The reaction was stirred and refluxed for 16 hours, and then it was poured into water. The aqueous mixture was extracted with diethyl ether, the extract was dried ($MgSO_4$), and the solution ,was concentrated to afford

an oil, which upon evacuation solidified to a white solid (50.2 g). An 8.0 g sample was flash chromatographed on silica gel with 50% ethyl acetate-hexane as eluent. Concentration of appropriate fractions gave 2.7 g (37%) of 4-(3-chloropropoxy)-3-methoxybenzaldehyde as a white solid m.p.=53°-55° C.

ANALYSIS

Calculated for $C_{11}H_{13}ClO_3$: 57.78% C 5.73% H.

Found: 57.21% C 5.52% H.

EXAMPLE 110

6-Fluoro-3-(3-pyrrolidinyl)-1,2-benzisoxazole hydrochloride

A mixture of 3-(6-fluoro-1,2-benzisoxazol-3-yl)-1-pyrrolidinylcarboxylic acid ethenyl ester (5.1 g, 18.4 mmol, hydrochloric acid (5 ml), and isopropyl alcohol (50 ml) was heated at reflux for 3.5 hr. At the end of the reaction, the solvent was reduced to about 30 ml on a rotary evaporator and the mixture was cooled to 0° C. for 2 hr. The crystals were collected by filtration and rinsed with cold isopropyl alcohol. The 6-fluoro-3-(3-pyrrolidinyl)-1,2-benzisoxazole hydrochloride product weighed 3.09 g (69%), m.p.=225°-227° C.

ANALYSIS

Calculated for $C_{11}H_{11}FN_2O.HCl$: 54.44% C 4.99% H 11.54% N.

Found: 54.35% C 4.99% H 11.38% N.

EXAMPLE 111

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3-hydroxyphenyl]ethanone

A mixture of N-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl-6-acetyl-2-benzoxazolinone (6.0 g, 0.014 mol) and 10% aqueous sodium hydroxide (50 ml) was stirred and refluxed for 40 minutes. Water was added and the reaction was made acidic with 5% hydrochloric acid. Saturated Na_2CO_3 was added until effervescence ceased. The aqueous mixture was extracted with dichloromethane. The dichloromethane extract was washed (water), dried (K_2CO_3) and concentrated to afford 2.6 g of a tacky solid. The crude solid was treated with saturated $NaHCO_3$, and extracted into dichloromethane The dichloromethane was washed (brine and then water), and dried ($MgSO_4$) yield. The organic extract was then concentrated to 2.4 g of a brown solid, which was combined with another sample to yield 5.0 g. This sample was flash chromatographed on silica. A small sample (0.25 g) was recrystallized from toluene to yield 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propylamino]-3-hydroxyphenyl]ethanone as a brownish solid, 0.15 g, m.p.=150°-152° C.

ANALYSIS

Calculated for $C_{23}H_{26}FN_3O_3$: 67.14% C 6.37% H 10.21% N.

Found: 67.54% C 6.58% H 9.95% N.

EXAMPLE 112

1-[3-Acetylamino-4-[3-chloropropoxy)phenyl]ethanone

A stirred mixture of 1-[3-acetylamino-4-hydroxyphenyl]ethanone (7.7 g, 0.04 mol), K_2CO_3 (5.7 g), 3-chloro-1-bromopropane (8.9 g, 0,056 mol), and acetone (100 ml) was refluxed for 16 hours. The reaction was allowed to cool to ambient temperature, and filtered. Concentration of the filtrate yielded 8.5 g of a white solid. The solid was recrystallized from toluene and then from ethanol to afford 6.5 g of an off-white solid. A 3.3 g sample of this material was flash chromatographed on silica gel. Concentration of the appropriate fractions afforded 2.8 g of a white solid. The solid was recrystallized from toluene and then from ethanol-water to yield 2.2 g (51%) of 1-[3-acetylamino-4-(3-chloropropoxy)phenyl] ethanone as a white solid, m.p.=124°-126° C.

ANALYSIS

Calculated for $C_{13}H_{16}ClNO_3$: 57.89% C 5.98% H 5.19% N.

Found: 57.08% C 5.85% H 5.13% N.

EXAMPLE 113

N-[2-(3-hydroxypropoxy)phenyl]acetamide

A stirred mixture of 2-hydroxyphenylacetamide (10.0 g, 0.066 mol), K_2CO_3 (6.9 g), 3-bromopropanol (12.8 g, 0.012 mol), and acetone (250 ml) was refluxed for 16 hours. The reaction mixture was allowed to cool, and then it was filtered. The filtrate was concentrated to yield 19.0 g of a thick, broom oil. The oil was distilled with a Kugelrohr apparatus and 11.2 g (82%) of a viscous, orange oil was collected. The oil solidified upon standing. An analytical sample was obtained by recrystallization from ethyl acetate to afford the alcohol as an off-white solid m.p.=78°-80° C.

ANALYSIS

Calculated for $C_{11}H_{15}NO_3$: 63.14% C 7.23% H 6.69% N.

Found: 63.10% C 7.32% H 6.64% N.

EXAMPLE 114

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl bromide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (12 in, 55 mmol), K_2CO_3 (13 m) and 1,4-dibromobutane (20 m, 9.3 mmol, 1.7 eq) in acetonitrile (300 ml) was stirred at room temperature overnight. The inorganic material was filtered. The solution was concentrated to ~80 ml, when crystals crashed out. The product was filtered to yield 14.16 m (73%), m.p.=243°-245° C.

ANALYSIS

Calculated for $C_{16}H_{20}BrFN_2O$: 54.09% C 5.67% H 7.89% N.

Found: 54.13% C 5.52% H 7.83% N.

EXAMPLE 115

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperindinyl-]ethyl acetate fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 gm, 13.6 mmol), K_2CO_3 (3.5 m, 25 mmol), 2-bromoethyl acetate (4 gm, 26.5 mmol) in acetonitrile (50 ml) was heated at reflux for 4 hr. After cooling to room temperature, the inorganic salts were filtered and washed with DCM (dichloromethane 50 ml). The organic solvent was removed on a rotary evaporator to give an oil. The oily product was purified on a flash chromatography column (60 gm of SiO_2; eluted with MeOH 2% -4% in DCM). The pure product thus obtained weighed 4.43 gm. This oil was dissolved in ethanol and treated with a solution of fumaric acid (1.2 gm) in ethanol. The salt crystallized out at room temperature to yield 3.44 gm (57%), m.p.=154°-155° C.

ANALYSIS

Calculated for $C_{16}H_{19}FN_2O_3.C_4H_4O_4$: 56.86% C 5.49% H 5.63% N.

Found: 56.75% C 5.41% H 6.54% N.

EXAMPLE 116

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]morpholine

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 gm, 13.6 mmol), 2-chloroethyl morpholine hydrochloride (4.46 gm, 29.7 mmol) and K_2CO_3 (7.3 gm, 2.2 eq) in acetonitrile (60 ml) was heated at reflux for 24 hr. The crude mixture was diluted with DCM and filtered. The solvent was concentrated to an oil (~7.1 gm). Purification on a silica gel column (55 gm, SiO_2, eluted with MeOH:DCM) yielded a solid product weighing 4 gm. Recrystallization from hot ethanol yielded 2.1 gm (48%), m.p. 131°–132° C.

ANALYSIS

Calculated for $C_{18}H_{24}FN_3O_2$: 64.84% C 7.26% H 12.60% N.

Found: 64.80% C 7.09% H 12.77% N.

EXAMPLE 117

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]phthalimide

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5 15 gm 23 4 mmol) K_2CO_3 (4.2 gm, 30.4 mmol) and 2-bromoethyl phthalimide (7.13 gm, 28 mmol) in acetonitrile (250 ml) was heated at reflux for 3.5 hr. The solids and solvent were removed. The residue was purified by flash chromatography (SiO_2, 110 m, eluted with 2–4% CH_3OH:DCM). The product thus obtained weighed 7.8 gm (84%). Part of the material was recrystallized to give 2.35 gm of off white crystals, m.p.=148°–149° C.

ANALYSIS

Calculated for $C_{22}H_{20}FN_3O_3$: 67.17% C 5.12% H 10.68% N.

Found: 67.01% C 5.20% H 10.76% N.

EXAMPLE 118

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl methyl ether fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.75 gm, 17 mmol), K_2CO_3 (3 gm, 21.7 mmol), bromoethyl methyl ether (2.84 gm, 20.4 mmol) in acetonitrile (150 ml) was heated at reflux for 3.5 hr. The reaction was cooled. The inorganics were filtered and rinsed with DCM. The organic solution was concentrated down to an oil (7 gm). Purification on a flash chromatography column (SiO_2, 45 gm; eluted with methanol/DCM) gave a light yellow oil as product (4 gm, 87%). This oil was dissolved into ethanol and treated with a solution of fumaric acid (1.67 gm) in ethanol (20 ml). White crystals (5.15 gm) were collected, m.p.=157°–158° C.

ANALYSIS

Calculated for $C_{15}H_{19}FN_2O_2.C_4H_4O_4$: 57.86% C 5.88% H 7.10% N.

Found: 57.53% C 5.94% H 6.94% N.

EXAMPLE 119

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl acetate fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (9.5 gm, 41 mmol), K_2CO_3 (7.2 gm, 51 mmol), and 4-bromobutyl acetate (10 gm, 51 mmol) in acetonitrile (200 ml) was heated at reflux for 3½ hr. At the end of the reaction, the solution was cooled and filtered. The inorganic salt was washed with DCM (50 ml). The organic solvent was removed. The residue was purified on a flash chromatography column (packed with Sorbsil C30 silica gel, 100 gm, eluted with DCM, 1 liter, increasing methanol from 2 to 4%, 2.51). The material thus purified weighed 12.92 gm (89%). A small sample (1.67 gm) was dissolved in ethanol and treated with 1 equivalent of fumaric acid (580 mg) in ethanol to yield white crystals: 1.8 gm, m.p.=142°–143° C.

ANALYSIS

Calculated for $C_{18}H_{23}FN_2O_3.C_4H_4O_4$: 58.66% C 6.04% H 6.22% N.

Found: 58.56% C 6.02% H 6.13% N.

EXAMPLE 120

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-butanol fumarate

A mixture of 4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl acetate (11.5 gm, 34.4 mmol), 15% NaOH (100 ml) and ethanol (100 ml) was heated at reflux for 4 hrs. After cooling to room temperature, the base was neutralized with HCl to pH=7. The solution was concentrated down to a small volume ml), then extracted with DCM. The DCM solution was washed with brine and dried over $MgSO_4$. The solvent was concentrated to give ~10 gm of crude oil. Purification by flash chromatography (Sorbsil C-30, 100 gm, eluted with MeOH:DCM, 3 liters) yielded 9.8 gm of white solid. The sample for testing was prepared by treatment of the free base (2.0 gm) with fumaric acid (780 mg. 1.0 eq) in ethanol. The crystals were collected and dried: 1.5 gm, m.p.=131°–132° C.

ANALYSIS

Calculated for $C_{16}H_{21}FN_2O_2.C_4H_4O_4$: 58.82% C 6.17% H 6.86% N.

Found: 58.81% C 6.37% H 6.66% N.

EXAMPLE 121

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl decanoate fumarate

To a solution of 4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butanol (2.0 gm, 6.84 mmol), triethylamine (1,0 gm, 10 mmol) in DCM (70 ml) decanoyl chloride (1.7 gm, 8.9 mmol) was added dropwise at room temperature. The mixture was stirred for 1 hr., then was concentrated to a crude solid. The solid was extracted into ethyl acetate, and the insoluble salts were filtered. The solvents were removed. The crude product was purified by flash chromatography (Sorbsil C-30, 30 in, eluted -with a mixture of MeOH in DCM). The oil thus obtained (2.5 gm, 81%) was converted to a fumarate salt with fumaric acid (650 mg), 1.0 eq) in ethanol. Crystals were collected: 1.48 gm, m.p.=109°–110° C.

ANALYSIS

Calculated for $C_{26}H_{39}FN_2O_3.C_4H_4O_4$: 64.04% C 7.70% H 4.98% N.

Found: 64.30% C 7.86% H 4.78% N.

EXAMPLE 122

3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propyl decanoate fumarate

To a solution 3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propanol (1.81 gm, 6.5 mmol) triethylamine (0.9 gm, 9.0 mmol) in DCM (45 ml) was added decanoyl chloride (1.5 gm, 7.8 mmol) dropwise at room tempera-

ture. The mixture was stirred for 20 minutes, then concentrated down to a crude solid. The solid was extracted into EtOAc (20 ml), and the insoluble salts were filtered. The EtOAc was removed. The crude oil was purified by flash chromatography (Sorbsil C-30, 30 gm; eluted with MeOH:DCM). The oil thus obtained (2.54 gm, 90%) was converted to a fumarate salt with fumaric acid (670 mg) in ethanol. The crystals collected weighed 1.61 gm, m.p.=100°–102° C.

ANALYSIS

Calculated for $C_{25}H_{27}FN_2O_3.C_4H_4O_4$: 63.52% C 7.54% H 5.11% N.

Found: 63.63% C 7.74% H 5.03% N.

EXAMPLE 123

N,N-Diethyl-4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl carbamate fumarate

To a mixture of 4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butanol (1.55 gm, 5.3 mmol) potassium t-butoxide (750 mg, 6.7 mmol) in THF (100 ml), diethylcarbamyl chloride (900 mg, 6.63 mmol) was added dropwise at room temperature. The mixture was stirred for 2 hr, then the solvent was removed. The residue was extracted into DCM. The DCM solution was washed with brine and dried over $MgSO_4$. The solution was concentrated. The product was purified on a flash chromatography column (SiO_2, 14 gm, eluted with 2% MeOH in DCM), to yield 1.84 gm of oil. This oil was dissolved into ethanol (~5 ml) and treated with a solution of fumaric acid (850 mg, 1.0 eq) in ethanol. Crystallization was induced with a small volume of isopropyl ether to produce 2.09 gm, m.p.=152°–153° C.

ANALYSIS

Calculated for $C_{21}H_{30}FN_3O_3.C_4H_4O_4$: 59.16% C 6.75% H 8.28% N.

Found: 59.17% C 6.84% H 8.16% N.

EXAMPLE 124

N-Methyl-4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butyl carbamate fumarate

To a mixture of 4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butanol (1.84 gm, 6.3 mmol), K_2CO_3 (850 mg) in chloroform, methyl isocyanate (448 mg, 7.7 mmol and 360 mg, 6.2 mmol) was added dropwise in two portions. The mixture was filtered and concentrated to a crude oil. Purification was done on a flash chromatography column (SiO_2, 11 gm, eluted with 2% CH_3OH in DCM) to yield a light yellow oil (2.05 gm, 93%). This oil was dissolved into ethanol and treated with a solution of fumaric acid (800 mg, 1.0 eq). Crystallization was induced with drops of isopropyl ether. Weight: 1.36 in, m.p.=96°–98° C.

ANALYSIS

Calculated for $C_{18}H_{24}FN_3O_3.C_4H_4O_4$: 56.76% C 6.06% H 9.02% N.

Found: 56.27% C 6.03% H 8.86% N.

EXAMPLE 125

2-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-1,3-dioxane fumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.0 gm, 9.1 mmol), K_2CO_3 (1.5 gm, 10.9 mmol) and bromoethyl-1,3-dioxane (2.1 gm, 10.7 mmol) in acetonitrile (50 ml) was heated at reflux for 3 hr. At the end, the insolubles were filtered and rinsed with DCM and the filtrate was evaporated down. The crude mixture was purified by flash chromatography over a silica gel column (Sorbsil C-30, 25 gm; eluted with DCM and MeOH (1–3%) in DCM). The fractions containing the pure product were combined and concentrated to give 3.13 gm of oil. The oil was treated with a fumaric acid (1.0 in) ethanol solution. The crystals were collected: 3.98 gm (77%), m.p.=161°–162° C.

ANALYSIS

Calculated for $C_{18}H_{23}FN_2O_3.C_4H_4O_4$: 58.66% C 6.04% H 6.22% N.

Found: 58.69% C 5.96% H 6.20% N.

EXAMPLE 126

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl-1-piperidinyl]ethanol hemifumarate

(A)

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl acetate

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl acetate was prepared according to Example 115.

(B)

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl-1-piperidinyl]ethanol hemifumarate

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl acetate (10.58 gm, 34.6 mmol), 15% NaOH (100 ml) and ethanol (100 ml) was heated at reflux for 4 hr. The solution was cooled (~5° C.) and neutralized with HCl to pH~7. The ethanol was removed under reduced pressure. The aqueous solution was basified with $NaHCO_3$ and extracted with DCM (2×200 ml). The DCM solution was washed with brine and dried over $MgSO_4$ and evaporated to give a white solid: 6.88 gm (75%). A sample (2.03 gm) was dissolved in ethanol and treated with fumaric acid (660 mg, 1.0 eq). Crystallization was induced with drops of isopropyl ether to yield off-white crystals: 1.43 in, m.p.=159°–161° C.

ANALYSIS

Calculated for $C_{14}H_{17}FN_2O_2.0.5C_4H_4O_4$: 59.62% C 5.94% H 8.69% N.

Found: 59.55% C 5.95% H 8.53% N.

EXAMPLE 127

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl decanoate fumarate.

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl alcohol (1.6 gm, 5 mmol) and triethylamine (800 mg, 8 mmoles) in chloroform (100 ml) was treated with decanoyl chloride (1.3 gm, 7.2 mmol) dropwise at room temperature. The mixture was stirred for 4 hours. The solvent was removed to leave a crude solid. The solid was dissolved into a small amount of DCM (15 ml), then was filtered. The solution was concentrated.

The purification was done by flash chromatography over a silica gel column (Sorbsil C-30, 30 gm; eluted with MeOH: DCM). The purified oil (2.45 gm, 95%) was treated with a fumaric acid (660 mg, 1.0 eq)/ethanol solution (15 ml). Crystallization was induced by adding drops of ether; yield: 1.97 gm, m.p.=109°–110° C.

ANALYSIS

Calculated for $C_{24}H_{35}FN_3O_3.C_4H_4O_4$: 62.90% C 7.35% H 5.24% N.

Found: 62.93% C 7.30% H 5.14% N.

EXAMPLE 128

N,N-Diethyl-2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylcarbamate fumarate

To a mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethanol (1.6 gm, 6 mmol) and potassium t-butoxide (850 mg, 7.6 mmol) in THF (100 ml) diethyl carbamyl chloride (1.03 gm, 7.5 mmol) was added dropwise at room temperature. The mixture was stirred for 4 hr. The reaction mixture was concentrated to a crude solid. The solid was dissolved in DCM and purified on a flash chromatography column (Sorbsil C-30, 27 gm; eluted with a MeOH: DCM mixture). The product thus purified as a light oil (2.2 gm, 91%) was dissolved into ethanol and treated with a fumaric acid (690 mg, 1.0 eq)/ethanol solution (15 ml). Crystallization on cooling yielded 2.15 gm of white crystals, m.p.=133°–135° C.

ANALYSIS

Calculated for $C_{19}H_{26}FN_3O_3.C_4H_4O_4$: 57.61% C 6.31% H 8.76% N.

Found: 57.49% C 6.25% H 8.54% N.

EXAMPLE 129

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine hemifumarate

(A)

2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl phthalimide

2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl phthalimide was prepared according to Example 117.

(B)

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1piperidinyl]ethylamine hemifumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl phthalimide (4.6 in, 11.7 mmol) and hydrazine monohydrate (1.17 gm, 23.4 mmol) in methanol (50 ml) was heated at reflux overnight. At the end of the reaction, methanol was removed to leave a crude solid. This was stirred with water (150 ml) and acidified with HCl to pH=2. The insolubles were filtered. The aqueous solution was basified with 50% NaOH then extracted with DCM (2×250 ml). The DCM solution was washed with brine and dried over $MgSO_4$. The solvent was removed to produce a colorless oil: 2.12 gm. This oil was treated with a solution of fumaric acid (935 mg, 1.0 eq) in ethanol. The salt crystallized out: 0.99 gm, 203°–205° C. A second crop of 0.73 in (m.p.=198°–200° C.) was collected later.

ANALYSIS

Calculated for $C_{14}H_{18}FN_3O.0.5C_4H_4O_4$: 59.80% C 6.27% H 13.07% N.

Found: 59.51% C 6.35% H 13.31% N.

EXAMPLE 130

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl decanamide fumarate

To a mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (1.49 gm, 5.5 mmol) and triethylamine (1.0 gm, 10 mmol) in chloroform (50 ml) decanoyl chloride (1.26 gm, 6.6 mmol) was added at room temperature. The mixture was stirred for 3 hr at room temperature. The solvent was stripped down to a crude mixture. This crude mixture was purified by flash chromatography over a silica gel column (SiO_2, 20 gm; eluded with a solution of MeOH (0–3%) in DCM). The fractions containing the pure product were pooled and concentrated to give 2.3 gm of oil. This oil was converted to a fumarate salt by treatment with fumaric acid (655 mg) in ethanol. The ethanol was concentrated down to a small volume and 3 volumes of isopropyl ether was added. This mixture was stirred overnight to cause crystallization. The solids were collected, weighed: 1.83 gm (60.5%), m.p.=108°–110° C.

ANALYSIS

Calculated for $C_{24}H_{36}FN_3O_2.C_4H_4O_4$: 63.02% C 7.56% H 7.87% N.

Found: 62.42% C 7.58% H 7.66% N.

EXAMPLE 131

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl acetamide fumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.56 g, 9.7 mmol) and triethylamine (1.45 gm, 14.5 mmol) in DCM (50 ml) was treated with dropwise addition of acetyl chloride (1.0 gm, 12.7 mmol) at room temperature. The mixture was stirred for 4 hr at room temperature. The reaction mixture was diluted with DCM and washed with brine. The organic solution was dried over $MgSO_4$ and concentrated to a crude oil. The crude oil was purified by flash chromatography over a silica gel column (SiO_2, 20 gm; eluted with (0–2%) CH_3OH in DCM). The pure product thus obtained weighed 1.36 gm (46%). It was converted to a fumarate salt by treatment with fumaric acid (517 mg) in ethanol. Recrystallization from ethanol gave white crystals; weight: 1.53 gm, m.p.=132°–133° C.

ANALYSIS

Calculated for $C_{16}H_{20}FN_3O_2.C_4H_4O_4$: 57.00% C 5.74% H 9.97% N.

Found: 57.05% C 5.85% H 9.95% N.

EXAMPLE 132

2-[[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]amino]ethyl acetate fumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.0 gm, 7.6 mmol), K_2CO_3 (1.38 gm, 10 mmol) and bromoethyl acetate (1.40 gm, 8.3 mmol) in acetonitrile (50 ml) was heated at reflux for 4 hr. At the end, the insolubles were filtered off and rinsed with DCM. The solvent was evaporated down. The crude mixture was purified by flash chromatography over a silica gel column (Sorbsil C-30, 30 gm; eluted with 2% CH_3OH in DCM, 800 ml). The oil (1.15 gm) thus obtained was treated with a solution of fumaric acid (358 mg) in ethanol. Crystallization was induced by adding drops of ethyl ether, yield: 1.09 gm, m.p.=116°–118° C.

ANALYSIS

Calculated for $C_{18}H_{24}FN_3O_3.C_4H_4O_4$: 56.77% C 6.06% H 9.03% N.

Found: 56.32% C 5.97% H 8.94% N.

EXAMPLE 133

Methyl N-[2-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]carbamate fumarate

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.0 gm, 7.6 mmol) and triethylamine (1.0 gm, 10 mmol) in DCM (50 ml) was treated with methyl chloroformate (860 mg, 9.12 mmol) dropwise at room temperature. The mixture was stirred for

1 hr. The reaction mixture was diluted with DCM and washed with brine. The organic solution was dried over $MgSO_4$ and concentrated to a crude oil. The purification was done by flash chromatography over a silica gel column (28 gm of Sorbsil C-30, eluted with DCM and MeOH/DCM). The pure oil thus obtained weighed 2.34 gm. It was converted to a fumarate salt by treatment with fumaric acid (840 mg, 1.0 eq) in ethanol. Crystallization was induced by adding drops of isopropyl ether, yield: 2.31 gm, m.p.=163°–165° C.

ANALYSIS

Calculated for $C_{16}H_{20}FN_3O_3.C_4H_4O_4$: 54.92% C 5.53% H 9.61% N.

Found: 54.49% C 5.45% H 9.24% N.

EXAMPLE 134

Z-2-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]hexahydro-1H-isoindole-1,3-dione fumarate

A mixture of 1-(2-aminoethyl)-4-(6-fluoro-1,2-benzisoxazol-3yl)piperidine (3.77 gm, 14.3 mmol) and cis-1,2-cyclohexanedicarboxylic anhydride (2.82 gm, 18.2 mmol, 1.25 eq) in dry pyridine (50 ml) was heated at 65° C. for 48 hr. The dark brown solution was concentrated to dryness on a rotary evaporator. The crude residue was purified twice by flash chromatography over a silica gel column (SiO_2, 45 gm and 50 gm, eluted with DCM and 1% CH_3OH in DCM). The pure product thus obtained 2.35 gm (41%), was converted to the fumarate salt by treatment with fumaric acid (660 mg) in ethanol. The crystals after two recrystallizations weighed 1.37 gm, m.p.=172°–173° C.

ANALYSIS

Calculated for $C_{22}H_{26}FN_3O_3.C_4H_4O_4$: 60.57% C 5.87% H 8.15% N.

Found: 60.40% C 5.55% H 7.82% N.

EXAMPLE 135

(S)-(+)-13-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol fumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (7.2 gm, 32.7 mmol), (S)-(+)-3-bromo-2-methyl-1-propanol (5.0 gm, 32.6 mmol), K_2CO_3(7.19 gm, 52 mmol) in acetonitrile (250 ml) was heated at reflux overnight. The insolubles were filtered off. The solvent was removed at reduced pressure and the crude residue was purified by silica gel chromatography (SiO_2, 84 gm, eluted with 21 of 1% CH_3OH in DCM) to give the target compound as an off-white solid (8.83 in, 94%). A sample of 1.7 gm was converted to the fumarate salt by treatment with fumaric acid (710 mg) in ethanol. Recrystallization from ethanol yielded 1.74 gm of white crystals, m.p.=119°–12.1° C.

ANALYSIS

Calculated for $C_{20}H_{25}FN_2O_6$: 58.82% C 6.17% H 6.86% N.

Found: 58.81% C 6.24% H 6.76% N.

EXAMPLE 136

4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-[3-(1-piperidinyl]-propyl]piperidine difumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (3.0 gm, 13.6 mmol), N-(3-chloropropyl)piperidine hydrochloride (4.05 gm, 20.4 mmol), K_2CO_3 (6 gm, 43.4 mmol), tetrabutyl-ammonium hydrogen sulfate (phase transfer catalyst, 2.3 gm) in acetonitrile (100 ml) and water (15 ml) was heated at reflux for 16 hr. The mixture was washed with brine and the layers were separated. The organic solution was concentrated. The crude product (6.4 gm) was purified by flash chromatography over a silica gel column (55 gm, sorbsil C-30; eluted with 2% CH_3OH:0°–5% DEA in DCM, 1.41). The oil thus purified (4.5 gm) was treated with fumaric acid (1.6 gm) in ethanol. The solid was collected: weight 3.1 in, m.p.178°– 181° C. Recrystallization from ethanol yielded 2.28 gm of white crystals, mp=190°–192° C.

ANALYSIS

Calculated for $C_{20}H_{24}FN_3O.2C_4H_4O_4$ 58.22% C 6.28% H 7.27% N.

Found: 58.39% C 6.36% H 7.34% N.

EXAMPLE 137

1-(3-Dimethylaminopropyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine difumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.05 gm, 13.8 mmol), 3-dimethylaminopropyl chloride hydrochloride (3.4 gm, 21 mmol), K_2CO_3(6.2 gm 45 mmol), tetrabutylammonium hydrogen sulfate (phase transfer catalyst, 1.5 gm) in acetonitrile (100 ml) and water (50 ml) was heated at 60° C. overnight. The aqueous phase was separated, and acetonitrile was removed at reduced pressure. The residue was extracted into DCM. The organic solution was washed with H_2O and brine, then dried with $MgSO_4$. The solvent was removed and the crude product (4.3 gm) was treated with fumaric acid (1.58 gm, 1.0eq) in dilute ethanol. The crystals were collected (2.53 gm), m.p.=192°–194° C. Recrystallization from ethanol yielded 2.08 gm of white crystals, mp=194°–195° C.

ANALYSIS

Calculated for $C_{17}H_{24}FN_3O_2.C_4H_4O_4$: 55.86% C 6.00% H 7.82% N.

Found: 56.11% C 5.94% H 7.86% N.

EXAMPLE 138

(R)-(−)-3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol fumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (14.5 gm, 65 mmol), K_2CO_3 (10 gm, 72 mmol). (R)-(-)-3-bromo-2-methyl-1-propanol (10 gm, 65.3 mmol), tetrabutylammonium hydrogen sulfate (1.27 gm, phase transfer catalyst) in acetonitrile (300 ml) and H_2O (5 ml) was heated at reflux for 6 hr. The mixture was cooled and the solvent was removed on rotary evaporator. The residue was extracted into methylene chloride (DCM), and the insolubles were filtered. After concentration of the extract, the crude product was purified by flash chromatography over a silica gel column (SiO_2, 150 gm; eluted with DCM, 11; 2% CH_3OH in DCM, 1.61). The material thus purified weighed 17 gm (89%). The sample for testing was prepared by treatment of a sample (2.28 gm) with fumaric acid (953 mg) in ethanol. The crystals formed slowly upon addition of isopropyl ether. These were collected and dried: weight 1.84 gm, m.p.=114°–115° C.

Elemental ANALYSIS

Calculated for $C_{16}H_{21}FN_2O_2.C_4H_4O_4$: 58.82% C 6.17% H 6.85% N.

Found: 58.48% C 6.08% H 6.57% N.

EXAMPLE 139

3-[1-[3-[4-(1-Methoxyethyl)-2-hydroxyphenoxyl]-propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (5.7 g, 26.0 mmol), 4-(3-chloropropoxy)-3-hydroxy-α-methylbenzenemethanol (6.0 g, 26.0 mmol), $NaHCO_3$ (2.4 g, 28.6 mmol), KI (200 mg) and CH_3CN (150 ml) was stirred at reflux under N_2 for 17 hours. A TLC showed a trace of the alkylating side chain, therefore additional 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (0.6 g, 2.7 mmol) and $NaHCO_3$ (0.22 g, 2.6 mmol) was added and the reaction was refluxed 3 hours longer. The cooled reaction was concentrated and the residue was partitioned between EtOAc and H_2O. The EtOAc extract was washed with H_2O then brine and after drying with $MgSO_4$ the extract was concentrated to yield 11.9 g of a beige oil. The sample was purified by preparative HPLC (Water's Associates Prep LC/System 500 utilizing 2 silica gel columns and eluting with 5% MeOH—CH_2Cl_2). Concentration of later fractions afforded 4.2 g of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylbenzenemethanol. Concentration of earlier fractions gave 4.0 g of a mixture of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylbenzenemethanol and 3-[1-[3-[4-(1-methoxyethyl)-2-hydroxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole (the latter was apparently formed by the reaction of the former with MeOH on silica gel).

The mixture was dissolved in anhydrous Et_2O (330 ml) and anhydrous MeOH (100 ml) and ethereal HCl was added. After stirring 1.5 hours, anhydrous Et_2O was added and the resultant solid was collected and dried to yield 2.9 g of a mixture of the respective HCl salts. The solid was suspended in H_2O and was basified with NH_4OH. The aqueous mixture was extracted with CH_2Cl_2 and the extract was washed with H_{20}, dried with $MgSO_4$ and concentrated to yield 2.7 g of a light beige oil. The oil was purified by preparative HPLC (Water's Associates Prep LC/System 500 using 2 silica gel columns and 3% MeOH—CH_2Cl_2 as eluent). Concentration of later fractions yielded 0.5 g of 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy-α-methylbenzenemethanol. Concentration of earlier fractions gave an oil that solidified upon standing. The product was triturated with heptane and filtered to yield 1.2 g of a white powder. The compound was recrystallized from EtOH to provide 1.1 g (10%) of 3-[1-[3-[4-(1-methoxyethyl)-2-hydroxyphenoxy]-propyl]-4-piperidinyl] -6-fluoro-1,2-benzisoxazole as clean white crystals m.p.=98°–100° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_2O_4$: 67.27% C 6.82% H 6.54% N. Found 67.18% C 6.84% H 6.54% N.

EXAMPLE 140

6-Fluoro-3-[1-[3-[(1H-indol-5-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.6 g, 11.8 mmol), K_2CO_3 (1.6 g, 11.6 mmol), KI (200 mg), 5-(3-chloropropoxy)indole (2.2 g, 10.5 mmol) and CH_3CN (100 ml) was stirred at reflux under N_2 for 18 hours. The cooled reaction was poured into H_2O and the aqueous mixture was extracted with EtOAc. The EtOAc extract was washed 2 times with H_2O, 2 times with brine and after drying with $MgSO_4$ the solvent was removed in vacuo to yield 5.1 g of a dark oil. The oil was purified by preparative HPLC (Water's Associates Prep LC/System 500, using 2 silica gel columns and 4% MeOH—CH_2Cl_2 as eluent) to afford 2.65 g (65%) of a beige solid. Recrystallization from ethanol gave 2.2 g (54%) of a beige powder, m.p.=118°–121° C.

ANALYSIS

Calculated for $C_{23}H_{24}FN_3O_2$: 70.21% C 6.15% H 10.68% N.

Found: 69.80% C 6.21% H 10.78% N.

EXAMPLE 141

6-Fluoro-3-[1-[3-[(isoquinol-5-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole sesquifumarate

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (2.8 g, 0.013 mol), 5-(3-chloropropoxy)isoquinoline (2.8 g, 0.013 mol), K_2CO_3 (1.7 g) and CH_3CN (50 ml) was refluxed for 16 h. The reaction was filtered and the filtrate was concentrated to an oil. The filter cake was treated with H_2O, and the aqueous suspension was extracted with CH_2Cl_2. The filtrate was also extracted with CH_2Cl_2, and the extracts were combined, washed (H_2O), dried (K_2CO_3) and concentrated to yield 5.4 g of a brown oil. The oil was purified by HPLC on silica gel columns, eluting with CH_2Cl_2/MeOH (5%), to afford 2.3 g of a yellow oil. The oil was dissolved in EtOAc and fumaric acid (0–66 g, 1 eq) was added. The mixture was refluxed briefly, and then stirred at ambient temperature for 16 h. The resulting white solid was collected to afford 2.2 g of the fumarate salt. The compound was recrystallized from DMF to yield 1.4 g (18.6%) of the isoquinoline as a sesquifumarate, m.p.=213°–215° C.

ANALYSIS

Calculated for $C_{30}H_{30}FN_3O_8$: 62.17% C 5.22% H 7.25% N.

Found: 62.01% C 5.11% H 7.28% N.

EXAMPLE 142

6-Fluoro-3-[1-[3-[(1-H-indol-4-yl)oxy]propyl]-4-piperidinyl]-1,2-benzisoxazole

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.5 g, 16 mmol), K_2CO_3 (2.2 g, 16 mmol), KI (200 mg), 4-(3-chloropropoxy)indole (3.0 g, 14 mmol) and CH_3CN (100 ml) was stirred at reflux under N_2 for 7 hours and then at ambient temperature for 68 hours. Reflux was resumed for an additional 6 hours whereupon a TLC revealed incomplete reaction. K_2CO_3 (0.5 g, 4 mmol) was added and the reaction was stirred at reflux for 17 hours. The cooled reaction was poured into H_2O and the aqueous mixture was extracted with EtOAc. The organic extract was washed with H_2O and saturated NaCl and after drying over $MgSO_4$ the solvent was removed to afford 5.7 g of a beige solid. The product was purified by preparative HPLC (Water's Associates Prep LC/System 500 using 2 silica gel columns and 4% MeOH—CH_2Cl_2 as eluent) to yield 3.4 g (61%) of a beige solid. Two consecutive recrystallizations from EtOH provided 2.3 g (41%) of a white powder, m.p.=129°–131° C.

ANALYSIS

Calculated for $C_{23}H_{24}FN_3O_2$: 70.21% C 6.15% H 10.68% N.

Found: 69.90% C 6.15% H 10.65% N.

EXAMPLE 143

6-Fluoro-3-[1-[3-[(6-methoxy-1H-indol-5-yl)oxy]-propyl]-4-piperidinyl]-1,2-benzisoxazole hemifumarate

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (3.0 g, 14 mmol), 5-(3-chloropropoxy)-6-methoxyindole (3.0 g, 13 mmol), K_2CO_3 (2.1 g, 14 mmol), KI (200 mg) and CH_3CN (150 ml) was stirred at reflux under N_2 for 48 hours. The cooled reaction was poured into H_2O and the aqueous mixture was extracted with EtOAc. The EtOAc extract was washed with H_2O and brine and was dried with $MgSO_4$. Removal of the solvent in vacuo gave 5.6 g of a dark oil. The oil was purified by preparative HPLC (Water's Associates Prep LC/System 500 using 2 silica gel columns and 2% Et_2NH-EtOAc as eluent) to yield 2.5 g (47%) of a beige solid. Recrystallization from EtOH afforded 2.0 g of an off White powder. A 1.8 g (4 mmol) sample was dissolved in warm EtOAc and fumaric acid (0.5 g, 4 mmol) was added. The reaction was stirred at ca 40° C. for 30 minutes and was then allowed to gradually cool to ambient temperature. The resultant hemifumarate salt was collected and dried to yield 2.0 g. The product was recrystallized from EtOH to provide 1.5 g (25%) of a light beige powder m.p.=186°–188° C.

ANALYSIS

Calculated for $C_{26}H_{28}FN_3O_5$: 64.84% C 5.87% H 8.73% N

Found: 64.22% C 5.85% H 8.55% N.

EXAMPLE 144

1-[4-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone

A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (2.4 g, 10.1 mmol), 1-[4-(3-chloropropoxy)-3-hydroxyphenyl]ethanone (2.5 g, 11.1 mmol), $NaHCO_3$ (0.94 g, 11.1 mmol), KI (100 mg) and CH_3CN (100 ml) was stirred at reflux under N_2 for 65 hours. The cooled reaction was poured into H_2O and the aqueous mixture was extracted with EtoAc. The EtoAc extract was washed with H_2O (1×) and brine (3×) and after drying with $MgSO_4$ the solvent was evaporated to give 4.2 g of a dark solid. Three consecutive recrystallizations from EtOH provided 2.1 g (48%) of glittery beige crystals m.p.=135°–137° C.

ANALYSIS

Calculated for $C_{23}H_{25}FN_2O_3S$: 64.47% C 5.88% H 6.54% N.

Found: 64.44% C 5.69% H 6.29% N.

EXAMPLE 145

4-[3-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-alpha-methylbenzenemethanol

To a stirred solution of 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]3-methoxyphenyl]ethanone (4.1 g, 9.3 mmol) in 60 ml MeOH-THF (1:1) under N_2 at ambient temperature, $NaBH_4$ (0.386 g, 10.2 mmol) was added portionwise. After complete addition, the reaction was stirred for 3.5 hours and was concentrated to yield a white gum. This was triturated with H_2O (2×) and the aqueous fraction was decanted away. Residual water was removed under high vacuum to afford 5.0 g of a white powder. The compound was taken up in boiling toluene and the insolubles were filtered away. Concentration of the toluene filtrate afforded 3.8 g of a beige solid. Purification via preparative HPLC (Water's Associates prep LC/System 500, using 2 silica gel columns and 2% Et_2NH-EtoAc) provided 2.7 g of a light beige solid. The product was recrystallized from EtoAc to afford 1.7 g (42%) of a pure white powder, m.p.=113°–115° C.

ANALYSIS

Calculated for $C_{24}H_{29}FN_2O_3S$: 64.84% C 6.58% H 6.30% N.

Found: 64.85% C 6.44% H 6.19% N.

EXAMPLE 146

(R)-(−)-3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propyl acetate fumarate

To a mixture of (R)-(-)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol (3.2 gm, 11 mmoles), triethylamine (3.2 gm, 11 mmoles) in DCM (100 ml), acetyl chloride (890 mg, 11.3 mmoles) was added dropwise at 0° C. The mixture was stirred at room temperature for 4½ hrs. The solvent was removed on a rotary evaporator. The triethylamine HCl salt was filtered off using a small amount of DCM. The crude product was dissolved in DCM was purified by flash chromatography over a silica gel column (SiO_2, 30 gm; eluted with DCM and 1% CH_3OH in DCM). The oil, thus purified, weighed 2.11 gm (58%). This oil was treated with a solution of fumaric acid (695mg, 1.0 eq.) in ethanol give the fumarate salt. Recrystallization from ethanol and isopropyl ether again yielded white crystals, 2.09 gm, m.p. 118°–120° C.

ANALYSIS

Calculated for $C_{18}H_{23}FN_2O_3.C_4H_4O_4$: 58.66% C 6.04% H 6.22% N.

Found: 58.53% C 5.76% H 8.91% N.

EXAMPLE 147

1-(R)-(−)-[4-[3-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl]ethanone fumarate

(A)

(R)-(−)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propyl methanesulfonate

To a mixture of (R)-(-)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol (7.26 gm, 24.8 mmoles), triethylamine (3ml, 30 mmoles) in methylene chloride (DCM, 120 ml), methanesulfonyl chloride (3.13 gm, 27.3 moles) was added dropwise at 0° C. The mixture was stirred at room temperature for 1 hr., then concentrated down to a crude mixture. Triethylamine hydrochloride salt was removed by filtration with DCM/ether as solvent. The crude oily mixture was purified with a flash chromatography column (SiO_2, 90 gm; eluted with DCM). The colorless oil, which is the methanesulfonate ester, weighed 6.48 gm (70%), and was used directly in the following step.

(B)

1(R)-(−)-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-proproxy]-3-ethoxyphenyl]ethanone fumarate

A solution of the above methanesulfonate (6.48 gm, 175 mmoles) in DMF (5 ml) was added in one portion to an aged (½ hr) cold mixture of acetovanillone (4.13 gm, 24.9 moles) and sodium hydride (670 mg, 26.5 moles) in DMF (40 ml) at 0° C. The resulting mixture was warmed to ~50° C. briefly and stirred at room temperature for 16 hrs. The mixture was extracted into DCM (500 ml) and washed twice with water, then brine. The

organic solution was dried over $MgSO_4$ and concentrated to an oil. This crude mixture was purified twice by flash chromatography over a silica gel column. The material thus purified weighed 5.37 gm. The fumarate salt was prepared by treatment of purified oil with fumaric acid (1.0 eq.) in ethanol and ether. Slightly off-white crystals were collected: 3.76 gm (38%), m.p.=141°–142° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2O_4.C_4H_4O_4$ 62.58% C 5.98% H 5.03% N.

Found: 62.52% C 5.75% H 4.96% N.

EXAMPLE 148

3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2,2-dimethyl-1-propanol fumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (3.0 gm, 13.6 mmoles), K_2CO_3 (12.5 gm, 17.5 mmoles), 3-bromo-2,2-dimethyl-1-propanol (3 gm, 21 mmoles, 1.5 eq.), tetrabutylammonium hydrogen sulfate (1 gm, phase transfer catalyst) in water (5 ml) and acetonitrile (150 ml) was heated at reflux for 43 days. TLC showed a small spot for the expected product. The mixture was diluted with EtOAc (400 ml) and washed with brine. The organic solution was dried and concentrated to a dark brown mixture. The crude mixture was purified carefully by flash chromatography (SiO_2, 95 gm to afford the dried pure product; 260 mg, (6%) as an oil. This oil was converted to the fumarate salt by treatment with fumaric acid (98.5 mg, 1.0 eq.) in ethanol. Recrystallization from ethanol:ether yielded 210 mg of white crystals, m.p.=144°–145° C.

ANALYSIS

Calculated for $C_{17}H_{23}FN_2O_2.C_4H_4O_4$: 59.70% C 6.44% H 6.63% N.

Found: 59.52% C 6.38% H 6.52% N.

EXAMPLE 149

1-(S)-(+)1[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl]ethanone fumarate

(A)

(S)-(+)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propyl methanesulfonate

To a mixture of (S)-(+)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propanol (8.8 gm, 30 mmoles), triethylamine (3.2 gm, 32 mmoles) in dichloromethane (DCM, 150 ml), methanesulfonyl chloride (4 gm, 35 mmoles) was added dropwise at 0° C. over 10 minutes. The mixture was stirred at room temperature for 1 hr, then concentrated. Triethylamine HCl salt was filtered off with a little DCM as solvent. The crude oil was purified with a flash chromatography column (SiO_2, 90 gm; eluted with DCM). The colorless oil thus purified weighed 5.28 in (47%) was used immediately in the following step.

(B)

1-(S)-(+)-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-proproxy]-3-methoxyphenyl]ethanone fumarate

A solution of (S)-(+)-3-[4-(6-fluoro-1,2-benzisoxazol-3-yl-1-piperidinyl]-2-methyl-1-propyl methanesulfonate (5.28 gm, 14.27 mmoles) in dimethylformamide (DMF, 10 ml) was added in one portion to an aged (1 hr) cold mixture of acetovanillone (3.55 in, 33.1 mmoles) and sodium hydride (530 mg, 22 moles) in DMF (35 ml) at 0° C. under N_2. The reaction was stirred overnight (16 hrs.) at room temperature. The mixture was diluted with EtOAc and washed with H_2O (2 times) and brine. The organic solution was dried and concentrated to an oil (9.4 gm). The crude oil mixture was purified by flash chromatography (SiO_2, 60 gm). The oil thus purified weighed 4.3 gm, (68%) and was converted to the fumarate salt (fumaric acid, 1.13 gm) in ethanol. Recrystallization from ethanol gave 1.36 gm of white crystals, m.p.=163°–165° C.

ANALYSIS

Calculated for $C_{25}H_{29}FN_2.O_4C_4H_4O_4$ 62.58% C 5.98% H 5.03% N.

Found: 62.40 % C 5.84% H 4.92% N.

EXAMPLE 150

2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl thioacetate fumarate

To a stirred solution of 0° C. of triphenlyphosphine (13.3 g, 0.05 mol) in THF (150 ml), diisopropyl-azodicarboxylate (10.2 ml, 0.05 mol) was added dropwise. After stirring at 0° C. for 0.5 h, a solution of 6-fluoro-3-[1-(2-hydroxyethyl)-4-piperidinyl]-1,2-benzisoxazole (8.5 g, 0.032 mol) and thioacetic acid (10.2 ml, 0.14 mol) in DMF (35 ml) was added dropwise. The reaction was then stirred at ambient temperature for 16 h, and then it ,was concentrated at 60° C., under vacuum, to yield a red oil. The oil was tritrated with H_2O, and then it was flash chromatographed on silica gel, eluting first with CH_2Cl_2 and then with 10% MeOH-CH—$_2Cl_2$. The appropriate fractions were concentrated to yield 16.5 g of an oil. The oil was tritrated with Et_2O and the solid (reaction by-products) that formed was removed by filtration. The filtrate was treated with fumaric acid (4.3 g), and 7.2 g of the fumarate salt of the desired product was obtained as an off white solid. The salt was recrystallized from EtOAc and then twice from EtOH to afford 1.0 g (7.0%) of the thioacetate as an off white solid, m.p.=118°–120° C.

EXAMPLE 151

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]-4,5-dichlorophthalimide

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.83 gm, 10.7 mmol) and 4,5-dichlorophthalic anhydride (2.56 gm, 11.93 mmol, 1.1 eq) in methylene chloride (100 ml, DCM) was stirred for 2 h, white solids precipitated and the TLC showed disappearance of the starting material. The solvent was removed, and the crude solid was loaded onto a flash chromatography column (28 gm, SiO_2, sorbsil C-30, eluted with 1% MeOH in DCM; 0.5% of NH_4OH was added towards the end of elution). The material thus purified weighed 2.26 gm as white crystals. Recrystallization twice from a large volume of hot ethanol (400 ml) yielded 1.57 gm of white shining crystals, m.p.=132°–134° C.

ANALYSIS

Calculated for $C_{22}H_{18}Cl_2FN_3O_3$: 57.16% C 3.92% H 9.09% N.

Found: 57.13% C 3.63% H 8.93% N.

EXAMPLE 152

N-[2-[4-(6-Fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]ethyl]phthalimide

A stirred mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisothiazole (4.72 g, 0.02 mole), potassium carbonate (4.14 g, 0.03 mole) and N-(2-bromoethyl)phthalimide (6.35 g, 0.025 mole) in 200 ml of acetonitrile is heated at reflux for 4 hours. The solids are then removed by filtration and the filtrate is concentrated under reduced pressure. The residue is purified by chromatography over silica gel to provide N-[2-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]ethyl]phthalimide.

EXAMPLE 153

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]-3,6-dichlorophthalimide

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.44 gm, 9.24 mmoles) and 3,6-dichlorophthalic anhydride (2.01 gm; 9.27 mmoles) in dichloromethane (DCM, 50 ml) was stirred at room temperature for 1 hr. White precipitates formed and the TLC of the reaction mixture showed that there was no starting amine remaining. The solvent was stripped down and the white solids which were poorly soluble in DCM were loaded onto a flash chromatography column, (SiO_2; 30 gm) and the column was eluted with a solution of 1% CH_3OH in DCM. The desired product thus obtained weighed 2.29 gm (54%). Recrystallization from hot ethanol yielded 2.15 gm of white crystals, m.p.=163°–164° C.

ANALYSIS

Calculated for $C_{22}H_{18}Cl_2FN_3O_3$: 57.16% C 3.92% H 9.09% N.

Found: 57.16% C 3.64% H 9.13% N.

EXAMPLE 154

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]-4-chlorophthalimide

A stirred mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.63 g, 0.01 mole) and 4-chlorophthalic anhydride (1.82 g, 0.01 mole) in dichloromethane (100 ml) is stirred at room temperature for 3 hours. The solvent is removed under reduced pressure and the residual material is purified by flash chromatography. The product was purified further by recrystallization to give N-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-chlorophthalimide.

EXAMPLE 155

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]-3-fluorophthalimide

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.37 gm, 8.98 mmoles), 3-fluorophthalic acid (1.82 in, 9.9 moles) and dicyclohexylcarbodiimide (DCC, 5.5 gm, 26.7 mmoles, 2.6 eq) in dichloromethane (DCM, 250 ml) was stirred at room temperature for 18 hrs. The solids were filtered off. The organic solution was concentrated down. The residue was purified on a flash chromatography column (SiO_2, 50 in; eluted with 1% CH_3OH:99% DCM, 1.4 liter; 2–6% CH_3OH:DCM, liter). The desired product thus obtained weighed 2.64 gm (71%) as an off-white solid. Recrystallization from hot ethanol gave 1.41 gm of white crystals, m.p.=142°–143° C.

ANALYSIS

Calculated for $C_{22}H_{19}F_2N_3O_3$: 64.22% C 4.66% H I0.21% N.

Found: 64.11% C 4.70% H 10.14% .

EXAMPLE 156

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]-4-fluorophthalimide

A stirred mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1piperidinyl]ethylamine (2.63 g, 0.01 mole) and 4-fluorophthalic anhydride (1.83 g, 0.011 mole) in dichloromethane (100 ml) is stirred at room temperature for 4 hours. The solvent is then removed under reduced pressure and the residual solids are purified by flash chromatography. The product is further purified by recrystallization to afford N-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-fluorophthalimide.

EXAMPLE 157

N-[2-[4-(6-Flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]-4-methylphthalimide

A mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.44 gm, 9.24 mmoles), 4-methylphthalic anhydride (1.76 gm, 10.8 moles) and dicyclohexylcarbodiimide (2.1 gm, 1.0 moles) in dichloromethane (DCM, 100 ml) was stirred at room temperature for 2 hr. The insolubles were filtered off. The DCM solution was concentrated to a crude solid. This was purified on a flash chromatography column (35 gm, SiO2, Sorbsil-C-30; eluted with 1% CH_3OH in 99% DCM). The material thus purified weighed 1.0 gm (26%) as a white solid. Recrystallization from hot ethanol gave 665 mg of crystals, m.p.=138°–140° C.

ANALYSIS

Calculated for $C_{23}H_{22}FN_3O_3$: 67.80% C 5.44% H 10.3! % N.

Found: 67.67% C 5.48% H 10.30% N.

EXAMPLE 158

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]-4-methoxyphthalimide

A stirred mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.63 g, 0.01 mole) and 4-methoxyphthalic anhydride (1.78 g, 0.01 mole) in dichloromethane (100 ml) is stirred at room temperature for 3 hours. The solvent is then removed under reduced pressure and the residual material is purified by flash chromatography. The product is purified further by recrystallization to give N-[2-[4-(6-fluoro-1,2-benzisoxazol-3yl)-1-piperidinyl]ethyl]-4-methoxyphthalimide.

EXAMPLE 159

N-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl-]ethyl]-4-nitrophthalimide

A stirred mixture of 2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethylamine (2.63 g, 0.01 mole) and 4-nitrophthalic anhydride (1.93 g, 0.01 mole) in dichloromethane (200 ml) is stirred at room temperature for 3 hours. The solvent is then removed under reduced pressure and the residual material is purified by flash chromatography. The product is purified further by recrystallization to give N-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-4-nitrophthalimide.

EXAMPLE 160

4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-2-hydroxybutane fumarate

To a solution of ethyl 3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propionate (3.21 gm, 10 mmoles) in tetrahydrofuran (THF, 100 ml), methylmagnesium bromide (10 ml, 30 moles, 3M solution in ether) was added dropwise over 15 minutes at room temperature under N_2. The resulting mixture was stirred for 16 hours. The mixture was slowly hydrolyzed with aqueous NH_4Cl solution. The THF solution was diluted with EtOAc (300 ml), then was washed with water and brine. The organic solution was separated and dried over $MgSO_4$. After removal of solvent, the crude product was purified by flash chromatography (25 gm, SiO_2; eluted with 1% CH_3OH:99% DCM). The material thus purified weighed 2.36 gm (77%) as white crystals. This was converted to the fumarate salt by treatment with fumaric acid (895 mg) in ethanol. Recrystallization from ethanol yielded white crystals, 2.47 gm, m.p.=156°-158° C.

ANALYSIS

Calculated for $C_{17}H_{23}FN_2O_2.C_4H_4O_4$: 59.70% C 6.44% H 5.63% N.

Found: 59.40% C 6.27% H 6.28% N.

EXAMPLE 161

Ethyl 3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propionate fumarate

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (5 gm, 22.7 mmoles), K_2CO_3 (3.8 gm, 27.5 mmoles) and ethyl bromopropionate (5 gm, 27.6 mmoles, 1.2 eq) in acetonitrile (200 ml) was heated at reflux for 16 hours. The mixture was cooled and filtered. The solvent was removed, and the residue was purified on a flash chromatography column (60 gm, SiO_2, eluted with DCM). The material thus purified weighed 7.27 gm (83%). The fumarate salt was prepared by treatment of the free base (2.17 gm) with fumaric acid (820 mg, 1.0 eq) in ethanol. Recrystallization from ethanol yielded 2.49 gm of white crystals, m.p.=135°-136° C.

ANALYSIS

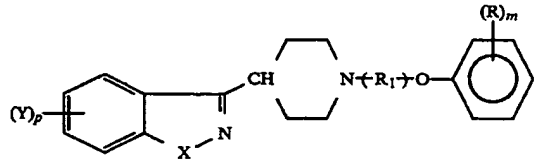
Calculated for $C_{17}H_{21}FN_2O_3.C_4H_4O_4$: 57.79% C 5.77% H 6.42% N.

Founded: 57.86% C 5.67% H 6.30% N.

This invention thus provides a group of chemical compounds that are capable of producing antipsychotic effects and may be capable of affecting negative symptoms of schizophrenia in a beneficial manner. In addition, many of the compounds may also have reduced tendencies to produce extrapyramidal side effects in mammals.

What is claimed is:

1. A compound of the formula:



wherein

X is —O— or —S—;

p is 1 or 2;

Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;

Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—;

(R_1) is R_{20}, R_{21}, or R_{22}, wherein:

R_{20} is $-(CH_2)_n-$ where n is 2, 3, 4 or 5;

R_{21} is

$-CH_2-CH=CH-CH_2-$,

$-CH_2-C\equiv C-CH_2-$,

$-CH_2-CH=CH-CH_2-CH_2$,

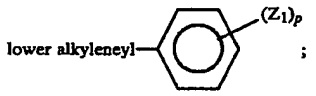
$-CH_2-CH_2-CH=CH-CH_2-$,

$-CH_2C\equiv C-CH_2-CH_2-$, or

$-CH_2-CH_2-C\equiv C-CH_2-$,

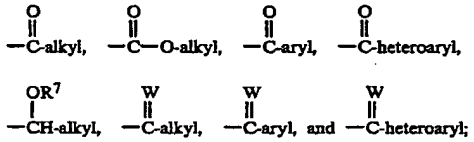
the —CH=CH— bond being cis or trans;

R_{22} is R_{20} or R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one C_1–C_6 linear alkyl group, phenyl group or



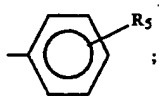
where Z_1 is lower alkyl, —OH, lower alkoxy, $-CF_3$, $-NO_2$, $-NH_2$ or halogen;

R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, formyl,



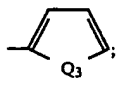
alkyl is lower alkyl;

aryl is phenyl or



where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;

heteroaryl is



Q_3 is —O—,

—CH=N—;

W is CH_2 or CHR_8 or N—R_9;

R_7 is hydrogen, lower alkyl, or acyl;

R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or —NHR_{10}; and

R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,

where aryl and heteroaryl are as defined above; and

m is 1, 2, or 3;

all geometric, optical and stereoisomers thereof, or a pharmaceutically acceptable acid addition salt thereof.

2. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

3. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

4. A compound as claimed in claim **1**, which is 1-[4-[4-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

5. A compound as claimed in claim **1**, which is 1-[4-[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

6. A compound as claimed in claim **1**, which is 1-[4-[2-[4-(1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

7. A compound as claimed in claim **1**, which is 1-[4-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

8. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

9. A compound as claimed in claim **1**, which is 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-α-methylbenzenemethanol or a pharmaceutically acceptable acid addition salt thereof.

10. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

11. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

12. A compound as claimed in claim **1**, which is 1-[4-[4-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-butoxy]-3-methoxyphenyl]ethanone fumarate or a pharmaceutically acceptable acid addition salt thereof.

13. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(5-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

14. A compound as claimed in claim **1**, which is 6-fluoro-3-[1-[3-(2-methoxyphenoxy)propyl]-4-piperidinyl]-1,2-benzisoxazole fumarate or a pharmaceutically acceptable acid addition salt thereof.

15. A compound as claimed in claim **1**, which is 1-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyphenyl]phenylmethanone or a pharmaceutically acceptable acid addition salt thereof.

16. A compound as claimed in claim **1**, which is 1-[4-[2-[4-(6-chloro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

17. A compound as claimed in claim **1**, which is 1-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]phenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

18. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-2-methylphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

19. A compound as claimed in claim **1**, which is 1-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-5-methylphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

20. A compound as claimed in claim **1**, which is N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyphenyl]acetamide or a pharmaceutically acceptable acid addition salt thereof.

21. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methylphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

22. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]phenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

23. A compound as claimed in claim **1**, which is 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzonitrile or a pharmaceutically acceptable acid addition salt thereof.

24. A compound as claimed in claim **1**, which is 1-[3,5-dibromo-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

25. A compound as claimed in claim **1**, which is 6-fluoro-3-[1-(3-phenoxypropyl)-4-piperidinyl]-1,2-benzisoxazole or a pharmaceutically acceptable acid addition salt thereof.

26. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl]-1-piperidinyl]-propoxy]-3-methylmercaptophenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

27. A compound as claimed in claim **1**, which is 1-[4-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperidinyl]butoxy]-3-methoxyphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

28. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]phenylmethanone or a pharmaceutically acceptable acid addition salt thereof.

29. A compound as claimed in claim **1**, which is 3-[1-[3-[4-(1-ethoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole or a pharmaceutically acceptable acid addition salt thereof.

30. A compound as claimed in claim **1**, which is 3-[1-[3-[4-(1-acetoxyethyl)-2-methoxyphenoxy]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole or a pharmaceutically acceptable acid addition salt thereof.

31. A compound as claimed in claim **1**, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]pentanone or a pharmaceutically acceptable acid addition salt thereof.

32. A compound as claimed in claim 1, which is 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-N-methylbenzeneamine or a pharmaceutically acceptable acid addition salt thereof.

33. A compound as claimed in claim 1, which is 3-[1-[3-(4-bromo-2-methoxyphenoxy)propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole or a pharmaceutically acceptable acid addition salt thereof.

34. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]propanone or a pharmaceutically acceptable acid addition salt thereof.

35. A compound as claimed in claim 1, which is 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxybenzamide or a pharmaceutically acceptable acid addition salt thereof.

36. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-(methylamino)phenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

37. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-ethoxphenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

38. A compound as claimed in claim 1, which is N-[2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]phenyl]acetamide, or a pharmaceutically acceptable acid addition salt thereof.

39. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-dimethylaminophenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

40. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-2-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

41. A compound as claimed in claim 1, which is 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxy-α-methylbenzene methanol, or a pharmaceutically acceptable acid addition salt thereof.

42. A compound as claimed in claim 1, which is 2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline, or a pharmaceutically acceptable acid addition salt thereof.

43. A compound as claimed in claim 1, which is N-[5-acetyl-2-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]acetamide, or a pharmaceutically acceptable acid addition salt thereof.

44. A compound as claimed in claim 1, which is 3-[1-[3-(4-ethyl-2-methoxyphenoxy)propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole, or a pharmaceutically acceptable acid addition salt thereof.

45. A compound as claimed in claim 1, which is 1-[3,5-dimethoxy-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]phenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

46. A compound as claimed in claim 1, which is N-[3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]phenyl]acetamide, or a pharmaceutically acceptable acid addition salt thereof.

47. A compound as claimed in claim 1, which is 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]aniline, or a pharmaceutically acceptable acid addition salt thereof.

48. A compound as claimed in claim 1, which is 3-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-4methoxyaniline, or a pharmaceutically acceptable acid addition salt thereof.

49. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methylaminophenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

50. A compound as claimed in claim 1, which is N-[3-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-4-methoxyphenyl]acetamide, or a pharmaceutically acceptable acid addition salt thereof.

51. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

52. A compound as claimed in claim 1, which is N,N-dimethyl-4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxybenzamide, or a pharmaceutically acceptable acid addition salt thereof.

53. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone oxime, or a pharmaceutically acceptable acid addition salt thereof.

54. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]methoxyphenyl]ethanone oxime O-methyl ether, or a pharmaceutically acceptable acid addition salt thereof.

55. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]ethanone hydrazone, or a pharmaceutically acceptable acid addition salt thereof.

56. A compound as claimed in claim 1, which is 6-fluoro-3-[1-[3-[2-methoxy-4-(1-methylethenyl)phenoxy]propyl]-4-piperidinyl]-1,2-benzisoxazole, or a pharmaceutically acceptable acid addition salt thereof.

57. A compound as claimed in claim 1, which is (Z)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2butenyl]oxy]-3-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

58. A compound as claimed in claim 1, which is (E)-1-[3-[4-[[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-4-hydroxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

59. A compound as claimed in claim 1, which is (E)-1-[3-[4-[[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2butenyl]oxy]-4-benzyloxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

60. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-Fluoro-1,2-benziosoxazol-3-yl)-1-piperidinyl]-propoxy]-3-bromophenyl]ethanone or a pharmaceutically acceptable acid addition salt thereof.

61. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxyphenyl]-2,2,2-trifluoroethanone, or a pharmaceutically acceptable acid addition salt thereof.

62. A compound as claimed in claim 1, which is 3-[1-[3-[4-(1-methoxyethyl)-2-hydroxyphenoxyl]propyl]-4-piperidinyl]-6-fluoro-1,2-benzisoxazole, or a pharmaceutically acceptable acid addition salt thereof.

63. A compound as claimed in claim 1, which is 1-[4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-hydroxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

64. A compound as claimed in claim 1, which is 4-[3-[4-(6-fluoro-1,2-benzisothiazol-3-yl)-1-piperidinyl]-propoxy]-3-methoxy-alpha-methylbenzenemethanol, or a pharmaceutically acceptable acid addition salt thereof.

65. A compound as claimed in claim 1, which is 1-(R)-(−)-[4-[3-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

66. A compound as claimed in claim 1, which is 1-(S-)(+)-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-methyl-1-propoxy]-3-methoxyphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

67. The compound of claim 1, wherein the pharmaceutically acceptable addition salt is selected from the group consisting of salts of mineral acids, salts of monobasic carboxylic acids, salts of dibasic carboxylic acids, and salts of tribasic carboxylic acids.

68. The compound of claim 67, wherein said pharmaceutically acceptable addition salts are selected from the group consisting of salts of hydrochloric acid, sulfuric acid, nitric acid, acetic acid, propionic acid, maleic acid, fumaric acid, carboxysuccinic acid, and citric acid.

69. The compound of claim 1, wherein Y is in the 5 position.

70. The compound of claim 1, wherein Y is in the 6 position.

71. The compound of claim 1, wherein Y is selected from the group consisting of hydrogen, chlorine, bromine and fluorine.

72. The compound of claim 71, wherein Y is fluorine.

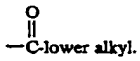
73. The compound of claim 72, wherein Y is in the 6 position.

74. The compound of claim 1, wherein p is 2, X is —O—, and Y is selected from the group consisting of lower alkoxy, hydroxy and halogen groups.

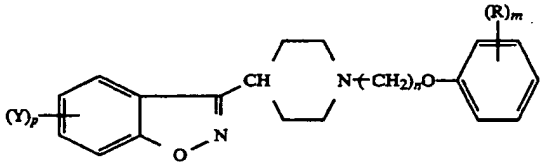
75. The compound of claim 74, wherein Y is a methoxy group.

76. The compound of claim 1, wherein R_1 is $—CH_2—CH=CH=CH_2—$.

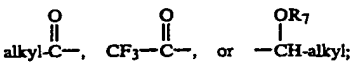
77. The compound of claim 1, wherein R is selected from the group consisting of hydrogen, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl, $—COCF_3$, C_1–C_6 alkanoyl, Cl, F, Br, I, C_1–C_3 alkylamino, $—NO_3$, $—CF_3$, $—OCF_3$, and



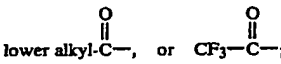
78. A compound of the formula:



wherein p is 1 or 2;
Y is hydrogen, Cl, Br, or F, when p is 1;
Y is lower alkoxy, hydroxy, or halogen when p is 2;
n is 2, 3, or 4;
R is hydrogen, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl, alkanoyl, Cl, F, Br, I, amino, C_1–C_3 mono or dialkyl amino, acylamino, $—NO_2$, $—OCF_3$, $—CF_3$,

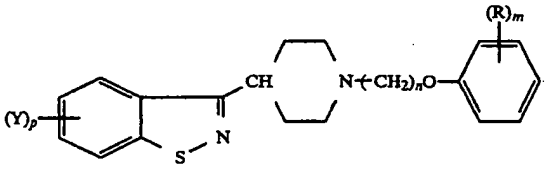


alkyl is lower alkyl;
R_7 is hydrogen, lower alkyl,

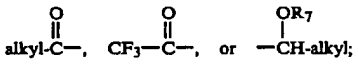


and
m is 1, 2, or 3;
all geometric, optical and stereoisomers thereof or a pharmaceutically acceptable acid addition salt thereof.

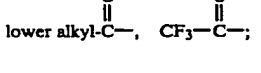
79. A compound of the formula:



wherein p is 1 or 2;
Y is hydrogen, Cl, Br, or F, when p is 1;
Y is lower alkoxy, hydroxy, or halogen when p is 2;
n is 2, 3, or 4;
R is hydrogen, C_1–C_3 alkyl, C_1–C_3 alkoxy, hydroxyl, acyl, alkanoyl, Cl, F, Br, I, amino, C_1–C_3 mono or dialkyl amino, acylamino, $—NO_2$, $—OCF_3$, $—CF_3$,

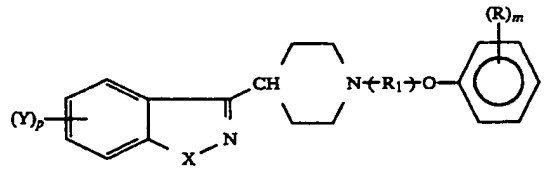


alkyl is lower alkyl;
R_7 is hydrogen, lower alkyl, or



and
m is 1, 2, or 3;
all geometric, optical and stereoisomers thereof or a pharmaceutically acceptable acid addition salt thereof.

80. A compound of the formula:



wherein
X is —O— or —S—;
p is 1 or 2;
Y is hydrogen, lower alkyl, hydroxy, chlorine, fluorine, bromine, iodine, lower alkoxy, trifluoromethyl, nitro, or amino, when p is 1;
Y is lower alkoxy, hydroxy and halogen when p is 2 and X is —O—,
is $—(CH_2)_n—$ where n is 2, 3, 4 or 5;

(R_1) is R_{20}, R_{21}, or R_{22}, wherein:

R_{20} is $-(CH_2)_n-$ where n is 2, 3, 4 or 5;

R_{21} is

$-CH_2-CH=CH-CH_2-$,

$-CH_2-C\equiv C-CH_2-$,

$-CH_2-CH=CH-CH_2-CH_2-$,

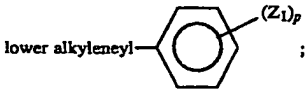
$-CH_2-CH_2-CH=CH-CH_2-$,

$-CH_2-C\equiv C-CH_2-CH_2-$, or

$-CH_2-CH_2-C=C-CH_2-$,

the $-CH=CH-$ bond being cis or trans;

R_{22} is R_{20} or R_{21} in which one or more carbon atoms of R_{20} or R_{21} are substituted by at least one C_1–C_6 linear alkyl group, phenyl group or

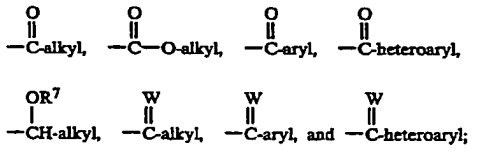


;

where Z_1 is lower alkyl, —OH, lower alkoxy, $-CF_3$, $-NO_2$, $-NH_2$ or halogen; and R and m are as defined hereinafter;

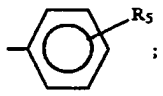
m is 1, 2, or 3; and

when m is 1, 2, or 3, R is hydrogen, lower alkyl, lower alkoxy, hydroxyl, carboxyl, chlorine, fluorine, bromine, iodine, amino, lower mono or dialkylamino, nitro, lower alkyl thio, trifluoromethoxy, cyano, acylamino, trifluoromethyl, trifluoroacetyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, formyl,



alkyl is lower alkyl;

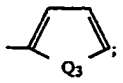
aryl is phenyl or



;

where R_5 is hydrogen, lower alkyl, lower alkoxy, hydroxy, chlorine, fluorine, bromine, iodine, lower monoalkylamino, lower dialkylamino, nitro, cyano, trifluoromethyl, trifluoromethoxy;

heteroaryl is



;

Q_3 is —O—, —S—,

,

$-CH=N-$;

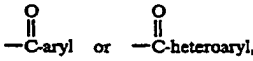
W is CH_2 or CHR_8 or $N-R_9$;

R_7 is hydrogen, lower alkyl, or acyl;

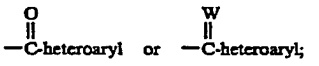
R_8 is lower alkyl;

R_9 is hydroxy, lower alkoxy, or $-NHR_{10}$; and

R_{10} is hydrogen, lower alkyl, C_1–C_3 acyl, aryl,



where aryl and heteroaryl are as defined above; and when m is 3, R is not



all geometric, optical and stereoisomers thereof, or pharmaceutically acceptable acid addition salt thereof.

81. A compound as claimed in claim **1**, which is (E)-1-[4-[[4-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]-2-butenyl]oxy]-3-methoxphenyl]ethanone, or a pharmaceutically acceptable acid addition salt thereof.

82. A pharmaceutical composition, which comprises compound as claimed in any one of claims **1–81**, and a pharmaceutically acceptable carrier therefor.

83. An antipsychotic composition which comprises a compound as claimed in any one of claims **1–81**, in an amount sufficient to produce an antipsychotic effect, and a pharmaceutically acceptable carrier therefor.

84. A method of treating psychoses, which comprises administering to a mammal a psychoses-treating effective amount of a compound as claimed in any one of claims **1–81**.

85. An analgesic composition which comprises a compound as claimed in any one of claims **1–81**, in an amount sufficient to produce a pain-relieving effect, and a pharmaceutically acceptable carrier therefor.

86. A method of alleviating pain, which comprises administering to a mammal a pain-relieving effective amount of a compound as claimed in any one of claims **1–81**.

* * * * *

EXHIBIT 4

VANDA
PHARMACEUTICALS INC.

Aventis Holdings Inc.
3711 Kennett Pike
Greenville, DE 19807

June 8, 2009

Dear Sir/Ms.:

On behalf of Vanda Pharmaceuticals, Marketing Applicant for New Drug Application No. 22-192 for FANAPT™ (iloperidone), its predecessors, and affiliates, I hereby authorize the patent owner of record, Aventis Holdings, Inc., in connection with its application for extension of U.S. Patent RE39,198, to rely upon the activities of Vanda Pharmaceuticals, and its predecessors and affiliates, undertaken in connection with seeking approval by the Food and Drug Administration of NDA No. 22-192. Vanda Pharmaceuticals is a licensee of the Aventis Holdings, Inc. under the patent.

Very truly yours,

Mihael H. Polymeropoulos, M.D.
Chief Executive Officer

EXHIBIT 5

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/712,129	11/15/2000	Joseph T. Strupczewski	USHR-1161 US REI 1

CONFIRMATION NO. 8800

POA ACCEPTANCE LETTER

5487
ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

OC000000036027473

Date Mailed: 05/19/2009

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/07/2009.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/deelliott/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

EXHIBIT 6

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-192

NDA APPROVAL

Vanda Pharmaceuticals
Attention: John Feeney, M.D.
Acting Chief Medical Officer
9605 Medical Center Drive
Suite 300
Rockville, MD 20850

Dear Dr. Feeney:

Please refer to your new drug application (NDA) dated and received September 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fanapt (iloperidone) 1, 2, 4, 6, 8, 10, and 12 mg tablets.

We acknowledge receipt of your submissions and communications dated November 6, 2008, November 19, 2008, January 9, 2009, March 10, 2009, March 17, 2009, April 15, 2009, and April 24, 2009.

Your submission of November 6, 2008 constituted a complete response to our July 25, 2008 action letter.

This new drug application provides for the use of Fanapt (iloperidone) for the acute treatment of schizophrenia in adults.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission **"SPL for approved NDA 22-192."**

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-192**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Psychiatry Products do not object to the use of the proprietary name, Fanapt, for this product.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 12 years because necessary studies are highly impractical due to the very low incidence of schizophrenia diagnosed prior to age 13.

We are deferring submission of your pediatric studies for ages 13 to 17 years for this application because the drug is ready for approval in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17. A study to obtain pharmacokinetic data and provide information pertinent to dosing of iloperidone tablets in the relevant pediatric population.

Final Protocol Submission:	by March 1, 2010
Study Completion Date:	by September 1, 2013
Final Report Submission:	by March 1, 2014

2. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17. A study of the efficacy and safety of iloperidone tablets in the relevant pediatric population.

Final Protocol Submission:	by March 1, 2010
Study Completion Date:	by September 1, 2013
Final Report Submission:	by March 1, 2014

Submit final reports to this NDA. Use the following designator to prominently label all submissions:

Required Pediatric Assessment(s)

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of carcinogenicity and to identify an unexpected serious risk of drug interactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3. Complete the ongoing P95 carcinogenicity study.

The timetable you submitted on April 24, 2009 states that you will conduct this study according to the following timetable:

Study Completion Date:	by February 28, 2010
Final Report Submission:	by May 31, 2010

4. Conduct a study investigating the possible in vitro interaction of iloperidone and P-Glycoprotein (P-Gp).

The timetable you submitted on April 15, 2009 states that you will conduct this study according to the following timetable:

Final Protocol Submission:	by August 1, 2009
Study Completion Date:	by October 1, 2009
Final Report Submission:	by November 1, 2009

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of Fanapt (iloperidone) to patients with hepatic dysfunction.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following clinical trial:

5. A repeat of your clinical trial CIL0522A0103, conducted with a group of subjects with mildly and moderately impaired hepatic function, comparing them to normals in the same trial.

The timetable you submitted on April 15, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission:	by November 1, 2009
Trial Completion Date:	by November 1, 2010
Final Report Submission:	by May 1, 2011

Submit clinical protocols to your IND for this product, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

REQUIRED POSTMARKETING PROTOCOL under 505(o)
REQUIRED POSTMARKETING FINAL REPORT under 505(o)
REQUIRED POSTMARKETING CORRESPONDENCE under 505(o)

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trial required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of the following postmarketing commitment agreed upon in our communication dated April 15, 2009:

6. Long-Term Efficacy Trial

You have agreed to conduct and submit the results of a randomized withdrawal clinical trial to address longer-term efficacy for your drug at appropriate doses.

Protocol Submission:	by November 1, 2009
Trial Completion Date:	by November 1, 2012
Final Report Submission:	by May 1, 2013

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

ADVISORY COMMITTEE

Your application was not referred to an advisory committee for review because this drug is not the first in its class, the clinical study design was acceptable, evaluation of the safety data did not reveal particular safety issues that were unexpected for this class and the efficacy trials did not pose particular concerns.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

DISSOLUTION METHOD AND SPECIFICATIONS

The dissolution method and specification for all strengths of the immediate release tablets should be:

Parameter	Dissolution Method and Specification
Apparatus Type	2 (rotating paddle)
Media	0.1 N HCl
Volume	500 ml
Frequency	50 rpm
Acceptance Criteria	80% in 30 minutes

EXPIRY

A 36 month expiry date is granted based on the available stability data.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301) 796-2201.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

FANAPT™

(iloperidone) Tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FANAPT safely and effectively. See full prescribing information for FANAPT.

FANAPT™ (iloperidone) tablets

Initial U.S. Approval: 2009

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. FANAPT is not approved for use in patients with dementia-related psychosis. (5.1)

INDICATIONS AND USAGE

FANAPT is an atypical antipsychotic agent indicated for the acute treatment of schizophrenia in adults (1). In choosing among treatments, prescribers should consider the ability of FANAPT to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate FANAPT slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration.

DOSAGE AND ADMINISTRATION

The recommended target dosage of FANAPT tablets is 12 to 24 mg/day administered twice daily. This target dosage range is achieved by daily dosage adjustments, alerting patients to symptoms of orthostatic hypotension, starting at a dose of 1 mg twice daily, then moving to 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7 respectively, to reach the 12 mg/day to 24 mg/day dose range. FANAPT can be administered without regard to meals. (2.1)

DOSAGE FORMS AND STRENGTHS

1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg tablets. (3)

CONTRAINDICATIONS

Known hypersensitivity to FANAPT or to any components in the formulation. (4)

WARNINGS AND PRECAUTIONS

- *Elderly patients with dementia-related psychosis who are* treated with atypical antipsychotic drugs are at an increased risk of death and cerebrovascular-related adverse events, including stroke. (5.1)
- *QT prolongation:* Prolongs QT interval and may be associated with arrhythmia and sudden death—consider using other antipsychotics first. Avoid use of FANAPT in combination with other drugs that are known to prolong QTc; use caution and consider dose modification when prescribing FANAPT with other drugs that inhibit FANAPT metabolism. Monitor serum potassium and magnesium in patients at risk for electrolyte disturbances (1, 5.2, 7.1, 7.3, 12.3)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation of drug and close monitoring. (5.3)
- *Tardive dyskinesia:* Discontinue if clinically appropriate. (5.4)
- *Hyperglycemia and diabetes mellitus:* Monitor glucose regularly in patients at risk for diabetes. (5.5)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold. (5.7)
- *Orthostatic hypotension:* Dizziness, tachycardia, and syncope can occur with standing. (5.8)
- *Leukopenia, Neutropenia, and Agranulocytosis* have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors. (5.9)
- *Suicide:* Close supervision of high risk patients. (5.13)
- *Priapism:* Cases have been reported in association with FANAPT treatment. (5.14)
- *Potential for cognitive and motor impairment*: Use caution when operating machinery. (5.15)
- See Full Prescribing Information for additional *WARNINGS and PRECAUTIONS.*

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence ≥5% and two-fold greater than placebo) were: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vanda Pharmaceuticals at 1-888-49VANDA (1-888-498-2632) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- The dose of FANAPT should be reduced in patients co-administered a strong CYP2D6 or CYP3A4 inhibitor. (2.2, 7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed. (8.1)
- Nursing Mothers: Should not breast feed. (8.3)
- Pediatric Use: Safety and effectiveness not established in children and adolescents. (8.4)
- Hepatic Impairment: Not recommended for patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

17.4 Interference with Cognitive and Motor Performance
17.5 Pregnancy
17.6 Nursing
17.7 Concomitant Medication
17.8 Alcohol
17.9 Heat Exposure and Dehydration

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of seventeen placebo controlled trials (modal duration 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristics(s) of the patients is not clear. FANAPT is not approved for the treatment of patients with Dementia-Related Psychosis. *[see Warnings and Precautions (5.1)]*

1 INDICATIONS AND USAGE

FANAPT™ tablets are indicated for the acute treatment of adults with schizophrenia *[see Clinical Studies (14)]*.

When deciding among the alternative treatments available for this condition, the prescriber should consider the finding that FANAPT is associated with prolongation of the QTc interval *[see Warnings and Precaution (5.2)]*. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia which can result in sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether FANAPT will cause torsade de pointes or increase the rate of sudden death is not yet known.

Patients must be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require a similar titration. Prescribers should be mindful of this delay when selecting an antipsychotic drug for the acute treatment of schizophrenia *[See Dosage and Administration (2.1) and Clinical Studies (14)]*.

The effectiveness of FANAPT in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use FANAPT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[See Dosage and Administration (2.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dose

FANAPT must be titrated slowly from a low starting dose to avoid orthostatic hypotension due to its alpha-adrenergic blocking properties. The recommended starting dose for FANAPT tablets is 1 mg twice daily. Increases to reach the target dose range of 6-12 mg twice daily may be made with daily dosage adjustments to 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, 10 mg twice daily, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively. Efficacy was demonstrated with FANAPT in a dose range of 6 to 12 mg twice daily. Prescribers should be mindful of the fact that patients need to be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require similar titration. Prescribers should also be aware that some adverse effects associated with FANAPT use are dose related.

The maximum recommended dose is 12 mg twice daily (24 mg/day); FANAPT doses above 24 mg/day have not been systematically evaluated in the clinical trials.

FANAPT can be administered without regard to meals.

2.2 Dosage in Special Populations

Dosage adjustments are not routinely indicated on the bases of age, gender, race, or renal impairment status *[see Use in Specific Populations (8.6, 8.7)]*.

Dosage adjustment for patients taking FANAPT concomitantly with potential CYP2D6 inhibitors: FANAPT dose should be reduced by one-half when administered concomitantly with strong CYP2D6 inhibitors such as fluoxetine or paroxetine. When the CYP2D6 inhibitor is withdrawn from the combination therapy, FANAPT dose should then be increased to where it was before *[See Drug Interactions (7.1)]*.

Dosage adjustment for patients taking FANAPT concomitantly with potential CYP3A4 inhibitors: FANAPT dose should be reduced by one-half when administered concomitantly with strong CYP3A4 inhibitors such as ketoconazole or clarithomycin. When the CYP3A4 inhibitor is withdrawn from the combination therapy, FANAPT dose should be increased to where it was before *[See Drug Interactions (7.1)]*.

Hepatic Impairment: FANAPT is not recommended for patients with hepatic impairment.

2.3 Maintenance Treatment

Although there is no body of evidence available to answer the question of how long the patient treated with FANAPT should be maintained, it is generally recommended that responding patients be continued beyond the acute response. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.4 Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address re-initiation of treatment, it is recommended that the initiation titration schedule be followed whenever patients have had an interval off FANAPT of more than 3 days.

2.5 Switching From Other Antipsychotics

There are no specific data to address how patients with schizophrenia can be switched from other antipsychotics to FANAPT or how FANAPT can be used concomitantly with other antipsychotics. Although immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

3 DOSAGE FORMS AND STRENGTHS

FANAPT tablets are available in the following strengths: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg.

The tablets are white, round, flat, beveled-edge and identified with a logo "  " debossed on one side and tablet strength "1", "2", "4", "6", "8", "10", or "12" debossed on the other side.

4 CONTRAINDICATIONS

FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product. Reactions have included pruritus and urticaria.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risks in Elderly Patients with Dementia-Related Psychosis

Increased Mortality

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

5.2 QT Prolongation

In an open-label QTc study in patients with schizophrenia or schizoaffective disorder (n=160), FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec.

No cases of torsade de pointes or other severe cardiac arrhythmias were observed during the pre-marketing clinical program.

The use of FANAPT should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thiordazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). FANAPT should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval; (5) recent acute myocardial infarction; and/or (6) uncompensated heart failure.

Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism *[see Drug Interaction (7.1)]*, and in patients with reduced activity of CYP2D6 *[see Clinical Pharmacology (12.3)]*.

It is recommended that patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. FANAPT should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 ms.

If patients taking FANAPT experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysarrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of this syndrome should include: (1) immediate discontinuation of the antipsychotic drugs and other drugs not essential to concurrent therapy, (2) intensive symptomatic treatment and medical monitoring, and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, which may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely on prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic administered increases, However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, FANAPT should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on FANAPT, drug discontinuation should be considered. However, some patients may require treatment with FANAPT despite the presence of the syndrome.

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because FANAPT was not marketed at the time these studies were performed, it is not known if FANAPT is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during

treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

5.6 Weight Gain

Based on the pooled data from the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the proportions of patients having a weight gain of ≥ 7% body weight was 12% for FANAPT 10-16 mg/day, 18% for FANAPT 20-24 mg/day, and 13% for FANAPT (combined doses) versus 4% for placebo. The mean weight change from baseline to endpoint in the short-term studies was -0.1 kg for placebo versus 2.0 kg for FANAPT-treated patients. Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg.

5.7 Seizures

In short-term placebo-controlled trials (4- to 6-weeks), seizures occurred in 0.1% (1/1344) of patients treated with FANAPT compared to 0.3% (2/587) on placebo. As with other antipsychotics, FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.8 Orthostatic Hypotension and Syncope

FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and, syncope. This reflects its α1-adrenergic antagonist properties. In double-blind placebo-controlled short-term studies, where the dose was increased slowly, as recommended above, syncope was reported in 0.4% (5/1344) of patients treated with FANAPT, compared with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20-24 mg/day, 3% of patients given 10-16 mg/day, and 1% of patients given placebo. More rapid titration would be expected to increase the rate of orthostatic hypotension and syncope.

FANAPT should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

5.9 Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue FANAPT and have their WBC followed until recovery.

5.10 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, FANAPT elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadalsteroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with FANAPT *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In a short-term placebo-controlled trial (4-weeks), the mean change from baseline to endpoint in plasma prolactin level for the FANAPT 24 mg/day-treated group was an increase of 2.6 ng/mL, compared to a decrease of 6.3 ng/mL in the placebo-group. In this trial, elevated plasma prolactin levels were observed in 26% of adults treated with FANAPT compared to 12% in the placebo group. In the short-term trials, FANAPT was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic agents. In pooled analysis from clinical studies including longer term trials, in 3210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0% in placebo-treated patients, and galactorrhea was reported in 8 female subjects (0.2%) compared to 3 female subjects (0.5%) in placebo-treated patients.

5.11 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing FANAPT for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.12 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. FANAPT and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Boxed Warning]*.

5.13 Suicide

The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for FANAPT should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

5.14 Priapism

Three cases of priapism were reported in the premarketing FANAPT program. Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. FANAPT shares this pharmacologic activity. Severe priapism may require surgical intervention.

5.15 Potential for Cognitive and Motor Impairment

FANAPT, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported in 11.9% (104/874) of adult patients treated with FANAPT at doses of 10 mg/day or greater versus 5.3% (31/587) treated with placebo. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The information below is derived from a clinical trial database for FANAPT consisting of 2070 patients exposed to FANAPT at doses of 10 mg/day or greater, for the treatment of schizophrenia. All of these patients who received FANAPT were participating in multiple-dose clinical trials. The conditions and duration of treatment with FANAPT varied greatly and included (in overlapping categories), open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions, reactions were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportions of individuals who experienced a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The information presented in these sections was derived from pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in patients who received FANAPT at daily doses within a range of 10 to 24 mg (n=874).

Adverse Reactions Occurring at an Incidence of 2% or More among FANAPT-Treated Patients and More Frequent than Placebo

Table 1 enumerates the pooled incidences of treatment-emergent adverse reactions that were spontaneously reported in four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, listing those reactions that occurred in 2% or more of patients treated with FANAPT in any of the dose groups, and for which the incidence in FANAPT-treated patients in any dose group was greater than the incidence in patients treated with placebo.

Table 1: Treatment-Emergent Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Trials in Adult Patients*

	Percentage of Patients Reporting Reaction		
Body System or Organ Class	**Placebo**	**FANAPT 10-16 mg/day**	**FANAPT 20-24 mg/day**
Dictionary-derived Term	**(N=587)**	**(N=483)**	**(N=391)**
Body as a Whole			
Arthralgia	2	3	3
Fatigue	3	4	6
Musculoskeletal Stiffness	1	1	3
Weight Increased	1	1	9
Cardiac Disorders			
Tachycardia	1	3	12
Eye Disorders			
Vision Blurred	2	3	1
Gastrointestinal Disorders			
Nausea	8	7	10
Dry Mouth	1	8	10
Diarrhea	4	5	7
Abdominal Discomfort	1	1	3
Infections			
Nasopharyngitis	3	4	3
Upper Respiratory Tract Infection	1	2	3
Nervous System Disorders			
Dizziness	7	10	20
Somnolence	5	9	15
Extrapyramidal Disorder	4	5	4
Tremor	2	3	3
Lethargy	1	3	1

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction Placebo (N=587)	 FANAPT 10-16 mg/day (N=483)	 FANAPT 20-24 mg/day (N=391)
Reproductive System			
Ejaculation Failure	<1	2	2
Respiratory			
Nasal Congestion	2	5	8
Dyspnea	<1	2	2
Skin			
Rash	2	3	2
Vascular Disorders			
Orthostatic Hypotension	1	3	5
Hypotension	<1	<1	3

*Table includes adverse reactions that were reported in 2% or more of patients in any of the FANAPT dose groups and which occurred at greater incidence than in the placebo group. Figures rounded to the nearest integer.

Dose-Related Adverse Reactions in Clinical Trials

Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, adverse reactions that occurred with a greater than 2% incidence in the patients treated with FANAPT, and for which the incidence in patients treated with FANAPT 20-24 mg/day were twice than the incidence in patients treated FANAPT 10-16 mg/day were: abdominal discomfort, dizziness, hypotension, musculoskeletal stiffness, tachycardia, and weight increased.

Common and Drug-Related Adverse Reactions in Clinical Trials

Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the following adverse reactions occurred in ≥5% incidence in the patients treated with FANAPT and at least twice the placebo rate for at least one dose: dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, orthostatic hypotension, and weight increased. Dizziness, tachycardia, and weight increase were at least twice as common on 20-24 mg/day as on 10-16 mg/day.

Extrapyramidal Symptoms (EPS) in Clinical Trials

Pooled data from the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies provided information regarding treatment-emergent EPS. Adverse event data collected from those trials showed the following rates of EPS-related adverse events as shown in Table 2.

Table 2: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (%) (N=587)	FANAPT 10-16 mg/day (%) (N=483)	FANAPT 20-24 mg/day (%) (N=391)
All EPS events	**11.6**	**13.5**	**15.1**
Akathisia	2.7	1.7	2.3
Bradykinesia	0	0.6	0.5
Dyskinesia	1.5	1.7	1.0
Dystonia	0.7	1.0	0.8
Parkinsonism	0	0.2	0.3
Tremor	1.9	2.5	3.1

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, there was no difference in the incidence of discontinuation due to adverse events between FANAPT-treated (5%) and placebo-treated (5%) patients. The types of adverse events that led to discontinuation were similar for the FANAPT- and placebo-treated patients.

Demographic Differences in Adverse Reactions in Clinical Trials

An examination of population subgroups in the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies did not reveal any evidence of differences in safety on the basis of age, gender or race *[see Warnings and Precautions (5.1)]*.

Laboratory Test Abnormalities in Clinical Trials

A between-group comparison of the pooled data from four placebo-controlled, 4- or 6-week studies, revealed no medically important differences between FANAPT and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry, including glucose. Similarly, there were no medically important changes in triglyceride and total cholesterol measurements (Table 3). There were no differences between FANAPT and placebo in the incidence of discontinuation due to changes in hematology, urinalysis, or serum chemistry.

Table 3: Change in Lipids Compared to Placebo

Mean change from baseline (mg/dL)	Placebo (N=587)	FANAPT 10-16 mg/day (N=483)	FANAPT 20-24 mg/day (N=391)
Triglycerides	-26.5	-26.5	-8.8
Total Cholesterol	-7.7	-3.9	3.9

In short-term placebo-controlled trials (4- to 6-weeks), there were 1.0% (13/1342) iloperidone-treated patients with hematocrit at least one time below the extended normal range during post-randomization

treatment, compared to 0.3% (2/585) on placebo. The extended normal range for lowered hematocrit was defined in each of these trials as the value 15% below the normal range for the centralized laboratory that was used in the trial.

Other Reactions during the Pre-marketing Evaluation of FANAPT

The following is a list of MedDRA terms that reflect treatment-emergent adverse reactions in patients treated with FANAPT at multiple doses ≥ 4 mg/d during any phase of a trial with the database of 3210 FANAPT-treated patients. All reported reactions are included except those already listed in Table 1, or other parts of the *Adverse Reactions (6)* section, those considered in the *Warnings and Precautions (5)*, those reaction terms which were so general as to be uninformative, reactions reported in fewer than 3 patients and which were neither serious nor life-threatening, reactions that are otherwise common as background reactions, and reactions considered unlikely to be drug related. It is important to emphasize that, although the reactions reported occurred during treatment with FANAPT, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not listed in Table 1 appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic Disorders: Infrequent – anemia, iron deficiency anemia; *Rare* – leukopenia

Cardiac Disorders: Frequent – palpitations; *Rare* – arrhythmia, atrioventricular block first degree, cardiac failure (including congestive and acute)

Ear and Labyrinth Disorders: Infrequent – vertigo, tinnitus

Endocrine Disorders: Infrequent – hypothyroidism

Eye Disorders: Frequent - conjunctivitis (including allergic); *Infrequent* – dry eye, blepharitis, eyelid edema, eye swelling, lenticular opacities, cataract, hyperemia (including conjunctival)

Gastrointestinal Disorders: Infrequent – gastritis, salivary hypersecretion, fecal incontinence, mouth ulceration; *Rare* - aphthous stomatitis, duodenal ulcer, hiatus hernia, hyperchlorhydria, lip ulceration, reflux esophagitis, stomatitis

General Disorders and Administrative Site Conditions: Infrequent – edema (general, pitting, due to cardiac disease), difficulty in walking, thirst; *Rare* - hyperthermia

Hepatobiliary Disorders: Infrequent – cholelithiasis

Investigations: Frequent: weight decreased; *Infrequent* – hemoglobin decreased, neutrophil count increased, hematocrit decreased

Metabolism and Nutrition Disorders: Infrequent – increased appetite, dehydration, hypokalemia, fluid retention

Musculoskeletal and Connective Tissue Disorders: Frequent – myalgia, muscle spasms; *Rare* – torticollis

Nervous System Disoders: Infrequent –paraesthesia, psychomotor hyperactivity, restlessness, amnesia, nystagmus; *Rare* – restless legs syndrome

Psychiatric Disorders: Frequent – restlessness, aggression, delusion; *Infrequent* – hostility, libido decreased, paranoia, anorgasmia, confusional state, mania, catatonia, mood swings, panic attack,

obsessive-compulsive disorder, bulimia nervosa, delirium, polydipsia psychogenic, impulse-control disorder, major depression

Renal and Urinary Disorders: Frequent – urinary incontinence; *Infrequent* – dysuria, pollakiuria, enuresis, nephrolithiasis; *Rare* – urinary retention, renal failure acute

Reproductive System and Breast Disorders: Frequent – erectile dysfunction; *Infrequent* – testicular pain, amenorrhea, breast pain; *Rare* – menstruation irregular, gynecomastia, menorrhagia, metrorrhagia, postmenopausal hemorrhage, prostatitis.

Respiratory, Thoracic and Mediastinal Disorders: Infrequent – epistaxis, asthma, rhinorrhea, sinus congestion, nasal dryness; *Rare* – dry throat, sleep apnea syndrome, dyspnea exertional

7 DRUG INTERACTIONS

Given the primary CNS effects of FANAPT, caution should be used when it is taken in combination with other centrally acting drugs and alcohol. Due to its α1-adrenergic receptor antagonism, FANAPT has the potential to enhance the effect of certain antihypertensive agents.

7.1 Potential for Other Drugs to Affect FANAPT

Iloperidone is not a substrate for CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. This suggests that an interaction of iloperidone with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for iloperidone metabolism. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., fluoxetine, paroxetine) can inhibit iloperidone elimination and cause increased blood levels.

Ketoconazole: Co-administration of ketoconazole (200 mg twice daily for 4 days), a potent inhibitor of CYP3A4, with a 3 mg single dose of iloperidone to 19 healthy volunteers, ages 18-45, increased the AUC of iloperidone and its metabolites P88 and P95 by 57%, 55% and 35%, respectively. Iloperidone doses should be reduced by about one-half when administered with ketoconazole or other strong inhibitors of CYP3A4 (e.g., itraconazole). Weaker inhibitors (e.g., erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level.

Fluoxetine: Co-administration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2-3 fold, and decreased the AUC of its metabolite P95 by one-half. Iloperidone doses should be reduced by one-half when administered with fluoxetine. When fluoxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to the previous level.

Paroxetine: Co-administration of paroxetine (20 mg/day for 5-8 days), a potent inhibitor of CYP2D6, with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 resulted in increased mean steady-state peak concentrations of iloperidone and its metabolite P88, by about 1.6 fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half. Iloperidone

doses should be reduced by one-half when administered with paroxetine. When paroxetine is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level. Other strong inhibitors of CYP2D6 would be expected to have similar effects and would need appropriate dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, iloperidone dose could then be increased to previous levels.

Paroxetine and Ketoconazole: Co-administration of paroxetine (20 mg once daily for 10 days), a CYP2D6 inhibitor, and ketoconazole (200 mg twice daily) with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 resulted in a 1.4 fold increase in steady-state concentrations of iloperidone and its metabolite P88 and a 1.4 fold decrease in the P95 in the presence of paroxetine. So giving iloperidone with inhibitors of both of its metabolic pathways did not add to the effect of either inhibitor given alone. Iloperidone doses should therefore be reduced by about one half if administered concomitantly with both a CYP2D6 and CYP3A4 inhibitor.

7.2 Potential for FANAPT to Affect Other Drugs

In vitro studies in human liver microsomes showed that iloperidone does not substantially inhibit the metabolism of drugs metabolized by the following cytochrome P450 isozymes: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, or CYP2E1. Furthermore, *in vitro* studies in human liver microsomes showed that iloperidone does not have enzyme inducing properties, specifically for the following cytochrome P450 isozymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5.

Dextromethorphan: A study in healthy volunteers showed that changes in the pharmacokinetics of dextromethorphan (80 mg dose) when a 3 mg dose of iloperidone was co-administered resulted in a 17% increase in total exposure and a 26% increase in Cmax of dextromethorphan. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.

Fluoxetine: A single 3 mg dose of iloperidone had no effect on the pharmacokinetics of fluoxetine (20 mg twice daily).

7.3 Drugs that Prolong the QT Interval

FANAPT should not be used with any other drugs that prolong the QT interval *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

FANAPT caused developmental toxicity, but was not teratogenic, in rats and rabbits.

In an embryo-fetal development study, pregnant rats were given 4, 16, or 64 mg/kg/day (1.6, 6.5, and 26 times the maximum recommended human dose [MRHD] of 24 mg/day on a mg/m^2 basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

In an embryo-fetal development study, pregnant rabbits were given 4, 10, or 25 mg/kg/day (3, 8, and 20 times the MRHD on a mg/m^2 basis) of iloperidone during the period of organogenesis. The highest dose caused increased early intrauterine deaths and decreased fetal viability at term; this dose also caused maternal toxicity.

In additional studies in which rats were given iloperidone at doses similar to the above beginning from either pre-conception or from day 17 of gestation and continuing through weaning, adverse reproductive effects included prolonged pregnancy and parturition, increased stillbirth rates, increased incidence of fetal visceral variations, decreased fetal and pup weights, and decreased post-partum pup survival. There were no drug effects on the neurobehavioral or reproductive development of the surviving pups. No-effect doses ranged from 4 to 12 mg/kg except for the increase in stillbirth rates which occurred at the lowest dose tested of 4 mg/kg, which is 1.6 times the MRHD on a mg/m^2 basis. Maternal toxicity was seen at the higher doses in these studies.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in rats, was given to pregnant rats during the period of organogenesis at oral doses of 20, 80, or 200 mg/kg/day. No teratogenic effects were seen. Delayed skeletal ossification occurred at all doses. No significant maternal toxicity was produced. Plasma levels of P95 (AUC) at the highest dose tested were 2 times those in humans receiving the MRHD of iloperidone.

There are no adequate and well-controlled studies in pregnant women. FANAPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and delivery

The effect of FANAPT on labor and delivery in humans is unknown.

8.3 Nursing mothers

FANAPT was excreted in milk of rats during lactation. It is not known whether FANAPT or its metabolites are excreted in human milk. It is recommended that women receiving FANAPT should not breast feed.

8.4 Pediatric use

Safety and effectiveness in pediatric and adolescent patients have not been established.

8.5 Geriatric use

Clinical Studies of FANAPT in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients. Of the 3210 patients treated with FANAPT in pre-marketing trials, 25 (0.5%) were ≥65 years old and there were no patients ≥75 years old.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile (i.e., increased risk in mortality and cerebrovascular events including stroke) in this population compared to younger patients with schizophrenia *[see Boxed Warning and Warnings and Precautions (5.1)]*. The safety and efficacy of FANAPT in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with FANAPT, vigilance should be exercised.

8.6 Renal impairment

Because FANAPT is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a significant impact on the pharmacokinetics of FANAPT. Renal impairment (creatinine clearance <30 mL/min) had minimal effect on maximum plasma concentrations (C_{max}) of iloperidone (given in a single dose of 3 mg) and its metabolites P88 and P95 any of the three analytes measured. $AUC_{0-\infty}$ was increased by 24%, decreased by 6%, and increased by 52% for iloperidone, P88 and P95, respectively, in subjects with renal impairment.

8.7 Hepatic impairment

A study in mild and moderate liver impairment has not been conducted. FANAPT is not recommended for patients with hepatic impairment.

8.8 Smoking Status

Based on *in vitro* studies utilizing human liver enzymes, FANAPT is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of FANAPT.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled substance

FANAPT is not a controlled substance.

9.2 Abuse

FANAPT has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which a CNS active drug, FANAPT, will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of FANAPT misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human experience

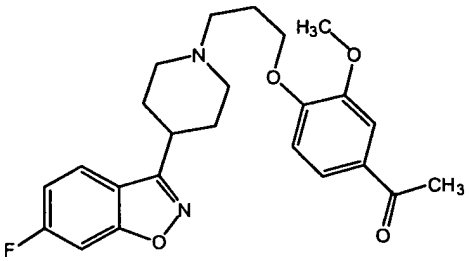
In pre-marketing trials involving over 3210 patients, accidental or intentional overdose of FANAPT was documented in eight patients ranging from 48 mg to 576 mg taken at once and 292 mg taken over a three-day period. No fatalities were reported from these cases. The largest confirmed single ingestion of FANAPT was 576 mg; no adverse physical effects were noted for this patient. The next largest confirmed ingestion of FANAPT was 438 mg over a four-day period; extrapyramidal symptoms and a QTc interval of 507 msec were reported for this patient with no cardiac sequelae. This patient resumed FANAPT treatment for an additional 11 months. In general, reported signs and symptoms where those resulting from an exaggeration of the known pharmacological effects (e.g., drowsiness and sedation, tachycardia and hypotension) of FANAPT.

10.2 Management of overdose

There is no specific antidote for FANAPT. Therefore appropriate supportive measures should be instituted. In case of acute overdose, the physician should establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of FANAPT. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of FANAPT, resulting in problematic hypotension. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of FANAPT-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision should continue until the patient recovers.

11 DESCRIPTION

FANAPT is a psychotropic agent belonging to the chemical class of piperidinyl-benzisoxazole derivatives. Its chemical name is 4'-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy]-3'-methoxyacetophenone . Its molecular formula is $C_{24}H_{27}FN_2O_4$ and its molecular weight is 426.48. The structural formula is:



Iloperidone is a white to off-white finely crystalline powder. It is practically insoluble in water, very slightly soluble in 0.1 N HCl and freely soluble in chloroform, ethanol, methanol, and acetonitrile.

FANAPT tablets are intended for oral administration only. Each round, uncoated tablet contains 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg of iloperidone. Inactive ingredients are: lactose monohydrate, microcrystalline cellulose, hydroxypropylmethylcellulose, crospovidone, magnesium stearate, colloidal silicon dioxide, and purified water (removed during processing). The tablets are white, round, flat, beveled-edge and identified with a logo "  " debossed on one side and tablet strength "1", "2", "4", "6", "8", "10", or "12" debossed on the other side.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

The mechanism of action of FANAPT, as with other drugs having efficacy in schizophrenia, is unknown. However it is proposed that the efficacy of FANAPT is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) antagonisms.

12.2 Pharmacodynamics

FANAPT exhibits high (nM) affinity binding to serotonin $5\text{-}HT_{2A}$ and dopamine D_2 and D_3 receptors (K_i values of 5.6, 6.3, 7.1 nM, respectively). FANAPT has moderate affinity for dopamine D_4, serotonin $5\text{-}HT_6$ and $5\text{-}HT_7$, and norepinephine $NE_{\alpha 1}$ receptors (K_i values of 25, 43, 22, and 36 nM respectively), and low affinity for the serotonin $5\text{-}HT_{1A}$, dopamine D_1, and histamine H_1 receptors (K_i values of 168, 216 and 473 nM, respectively). FANAPT has no appreciable affinity (K_i>1000 nM) for cholinergic muscarinic receptors. FANAPT functions as an antagonist at the dopamine D_2, D_3, serotonin $5\text{-}HT_{1A}$ and norepinephrine α_1/α_{2C} receptors. The affinity of the FANAPT metabolite P88 is generally equal or less than that of the parent compound. In contrast, the metabolite P95 only shows affinity for $5\text{-}HT_{2A}$ (K_i value of 3.91) and the $NE_{\alpha 1A}$, $NE_{\alpha 1B}$, $NE_{\alpha 1D}$, and $NE_{\alpha 2c}$ receptors (K_i values of 4.7, 2.7, 8.8 and 4.7 nM respectively).

12.3 Pharmacokinetics

The observed mean elimination half-lives for iloperidone, P88 and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26 and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37 and 31 hours, respectively. Steady-state concentrations are attained within 3-4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics. The pharmacokinetics of iloperidone is more than dose proportional. Elimination of iloperidone is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

Absorption: Iloperidone is well absorbed after administration of the tablet with peak plasma concentrations occurring within 2 to 4 hours; while the relative bioavailability of the tablet formulation compared to oral solution is 96%. Administration of iloperidone with a standard high-fat meal did not significantly affect the Cmax or AUC of iloperidone, P88, or P95, but delayed Tmax by 1 hour for iloperidone, 2 hours for P88 and 6 hours for P95. FANAPT can be administered without regard to meals.

Distribution: Iloperidone has an apparent clearance (clearance / bioavailability) of 47 to 102 L/h, with an apparent volume of distribution of 1340-2800L. At therapeutic concentrations, iloperidone and its metabolites are ~95% bound to serum proteins.

Metabolism and Elimination: Iloperidone is metabolized primarily by three biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and *O*-demethylation (mediated by CYP3A4). There are two predominant iloperidone metabolites, P95 and P88. The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively.

Approximately 7-10% of Caucasians and 3-8% of Black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive or ultrarapid metabolizers. Co-administration of FANAPT with known strong inhibitors of

CYP2D6 like fluoxetine results in a 2.3 fold increase in iloperidone plasma exposure, and dosing adjustment is needed.

Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with EMs. Laboratory tests are available to identify CYP2D6 PMs and dosing adjustments should be considered in this group of patients.

The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Lifetime carcinogenicity studies were conducted in CD-1 mice and Sprague Dawley rats. Iloperidone was administered orally at doses of 2.5, 5.0 and 10 mg/kg/day to CD-1 mice and 4, 8 and 16 mg/kg/day to Sprague Dawley rats (0.5, 1.0 and 2.0 times and 1.6, 3.2 and 6.5 times, respectively, the maximum recommended human dose [MRHD] of 24 mg/day on a mg/m^2 basis). There was an increased incidence of malignant mammary gland tumors in female mice treated with the lowest dose (2.5 mg/kg/day) only. There were no treatment-related increases in neoplasia in rats.

Proliferative and/or neoplastic changes in the mammary gland of rodents have been observed following the chronic administration of antipsychotic drugs and are considered to be prolactin mediated. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with iloperidone.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in mice or rats, was given orally to Wistar rats for 26 weeks at doses of 50 or 500 mg/kg/day. Although this study was not adequate for assessment of carcinogenic potential, proliferative responses were seen in several organs: mammary gland hyperplasia in males and females, thyroid follicular hyperplasia in females, ovarian interstitial cell hyperplasia, pituitary cell proliferation in males, and endocrine pancreas proliferation in males and females. The above were seen at both doses except for the ovarian and pancreas effects which were seen at the higher dose only. Plasma levels of P95 (AUC) at the lower dose were 2.5 times those in humans receiving the MRHD of iloperidone, but as indicated above a no-effect dose for the proliferative responses was not determined. It is not known if these proliferative responses will progress to neoplasia with longer term treatment.

Mutagenesis: Iloperidone was negative in the Ames test and in the *in vivo* mouse bone marrow and rat liver micronucleus tests. Iloperidone induced chromosomal aberrations in Chinese Hamster Ovary (CHO) cells *in vitro* at concentrations which also caused some cytotoxicity.

The iloperidone metabolite P95 was negative in the Ames test, the V79 chromosome aberration test, and an *in vivo* mouse bone marrow micronucleus test.

Impairment of Fertility: Iloperidone decreased fertility at 12 and 36 mg/kg in a study in which both male and female rats were treated. The no-effect dose was 4 mg/kg, which is 1.6 times the maximum recommended human dose of 24 mg/day on a mg/m^2 basis.

14 Clinical Studies

The efficacy of FANAPT in the treatment of schizophrenia was supported by two placebo- and active-controlled short-term (4- and 6-week) trials. Both trials enrolled patients who met the DSM-III/IV criteria for schizophrenia.

Two instruments were used for assessing psychiatric signs and symptoms in these studies. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia.

A 6-week, placebo-controlled trial (n=706) involved two dose ranges of FANAPT (12-16 mg/day or 20-24 mg/day) compared to placebo and an active control. This study involved titration of FANAPT starting 1 mg twice daily on day 1 and increasing to 2, 4, 6, 8, 10 and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, as needed. The primary endpoint was change from baseline on the BPRS total score at the end of treatment (Day 42). Both the 12-16 mg/day and the 20-24 mg/day dose ranges of FANAPT were superior to placebo on the BPRS total score. The active control antipsychotic drug appeared to be superior to FANAPT in this trial within the first 2 weeks, a finding that may in part be explained by the more rapid titration that was possible for that drug.

A 4-week, placebo-controlled trial (n=604) involved one fixed dose of FANAPT (24 mg/day) compared to placebo and an active control. The titration schedule for this study was similar to that for the 6-week study. This study involved titration of FANAPT starting 1 mg twice daily on day 1 and increasing to 2, 4, 6, 8, 10 and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7. The primary endpoint was change from baseline on the PANSS total score at the end of treatment (Day 28). The 24 mg/day FANAPT dose was superior to placebo in the PANSS total score. FANAPT appeared to have similar efficacy to the active control drug which also needed a slow titration to the target dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

FANAPT tablets are white, round and identified with a logo "  " debossed on one side and tablet strength "1", "2", "4", "6", "8", "10", or "12" debossed on the other side. Tablets are supplied in the following strengths and package configurations:

Package Configuration	Tablet Strength (mg)	NDC Code
Bottles of 60	1 mg	43068-101-02
Bottles of 60	2 mg	43068-102-02
Bottles of 60	4 mg	43068-104-02
Bottles of 60	6 mg	43068-106-02
Bottles of 60	8 mg	43068-108-02
Bottles of 60	10 mg	43068-110-02
Bottles of 60	12 mg	43068-112-02
Titration Pack	2x1 mg, 2x2 mg, 2x4 mg, 2x6 mg (Total of 8 tablets)	43068-113-04

Storage
Store FANAPT tablets at controlled room temperature, 25°C (77°F); excursions permitted to 15° - 30 °C (59° - 86°F) [See USP Controlled Room Temperature]. Protect FANAPT tablets from exposure to light and moisture.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe FANAPT:

17.1 QT interval Prolongation

Patients should be advised to consult their physician immediately if they feel faint, lose consciousness or have heart palpitations. Patients should be counseled not to take FANAPT with other drugs that cause QT interval prolongation *[see Warnings and Precautions (5.2)]*. Patients should be told to inform physicians that they are taking FANAPT before any new drug is taken.

17.2 Neuroleptic Malignant Syndrome

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

17.3 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.8)]*.

17.4 Interference with Cognitive and Motor Performance

Because FANAPT may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that FANAPT therapy does not affect them adversely *[see Warnings and Precautions (5.15)]*.

17.5 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with FANAPT *[see Use in Specific Population (8.1)]*.

17.6 Nursing

Patients should be advised not to breast-feed an infant if they are taking FANAPT *[see Use in Specific Population (8.3)]*.

17.7 Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see Drug Interactions (7)]*.

17.8 Alcohol

Patients should be advised to avoid alcohol while taking FANAPT.

17.9 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

FANAPT is a trademark of Vanda Pharmaceuticals Inc.

Distributed by Vanda Pharmaceuticals Inc. Rockville, MD 20850

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
5/6/2009 04:36:30 PM

EXHIBIT 7

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United States Patent and Trademark Office

Patent Bibliographic Data					05/05/2009 05:35 PM
Patent Number:	RE39198		**Application Number:**	09712129	
Issue Date:	07/18/2006		**Filing Date:**	10/30/1992	
Title:	HETEROARYLPIPERIDINES, PYRROLIDINES AND PIPERAZINES AND THEIR USE AS A				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):		No Maintenance History Found --- End of Maintenance History ---			
Address for fee purposes:	FINNEGAN, HENDERSON, FARABOW, GARRETT & LLP 901 NEW YORK AVENUE, NW WASHINGTON, DC 200014413				
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EXHIBIT 8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 36,827 Date MAY 3 1991

Hoechst-Roussel Pharmaceuticals, Inc.
Route 202-206, P.O. Box 2500
Somerville, New Jersey
08876-1258
Att: D. J. Bucceri
Vice-President
Drug Regulatory Affairs

HRPI/91/054

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: **36,827**

Sponsor: **Hoechst-Roussel Pharm., Inc.**

Name of Drug: **HP 873**

Date of Submission: **April 25,1991**

Date of Receipt: **May 1,1991**

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact **Mr. Tony DeCicco**
Consumer Safety Officer
(301) 443-3504

Sincerely yours,

John S. Purvis

John Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-120 - yellow
HFD-120/CSO - green

IND ACKNOWLEDGEMENT

EXHIBIT 9

From: Updegraff, Kimberly [Kimberly.Updegraff@fda.hhs.gov]
Sent: Monday, November 26, 2007 4:50 PM
To: Jennifer Hamilton
Cc: Updegraff, Kimberly
Subject: Iloperidone NDA 22-192

Dear Jennifer,

Please refer to your 9/27/2007 new drug application for the iloperidone tablets, NDA 22-192. We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed. Please note, our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

You will receive an official letter, delineating any requests or recommendations, by 12/11/2007.

Sincerely,

Kimberly Updegraff

Kimberly Updegraff, R.Ph., M.S.
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation
Phone: (301)796-2201
Fax: (301)796-9838
Email: Kimberly.Updegraff@fda.hhs.gov

EXHIBIT 10

IND#	Product Name	Submission No	Submission Date	Protocol	Sponsor	Submission Type
36,827	iloperidone tablets	269	10-Jun-08		Vanda	Annual Report
36,827	iloperidone tablets	268	5-Mar-08		Vanda	FDA Correspondence
36,827	iloperidone tablets	267	14-Jan-08	P95 Carc Protocol	Vanda	New Protocol
36,827	iloperidone tablets	266	24-Jul-07		Vanda	New Protocol
36,827	iloperidone tablets	265	29-Jun-07		Vanda	FDA Correspondence
36,827	iloperidone tablets	264	18-Jun-07		Vanda	Annual Report
36,827	iloperidone tablets	263	11-May-07		Vanda	New Protocol
36,827	iloperidone tablets	262	10-May-07		Vanda	Trade Name review
36,827	iloperidone tablets	261	11-Apr-07		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	15-Mar-07		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	7-Mar-07		Vanda	FDA Correspondence
36,827	iloperidone tablets	260	27-Feb-07		Vanda	Briefing book
36,827	iloperidone tablets	259	22-Feb-07		Vanda	FDA Correspondence
36,827	iloperidone tablets	258	9-Feb-07		Vanda	FDA Correspondence
36,827	iloperidone tablets	257	7-Feb-07		Vanda	Trade Name review
36,827	iloperidone tablets	256	7-Feb-07	3101	Vanda	IND Safety report
36,827	iloperidone tablets	n/a	7-Feb-07		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	1-Feb-07		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	30-Jan-07		Vanda	FDA Correspondence

36,827	iloperidone tablets	n/a	4-Jan-07	3101	Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	19-Dec-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	13-Dec-06	3101	Vanda	FDA Correspondence
36,827	iloperidone tablets	255	11-Dec-06		Vanda	Briefing book
36,827	iloperidone tablets	n/a	8-Dec-06	3101	Vanda	FDA Correspondence
36,827	iloperidone tablets	254	8-Dec-06		Vanda	IND Safety report
36,827	iloperidone tablets	n/a	4-Dec-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	30-Nov-06	3101	Vanda	7-day Safety Report
36,827	iloperidone tablets	253	30-Nov-06	3101	Vanda	Statistical Analysis Plan
36,827	iloperidone tablets	n/a	22-Nov-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	252	21-Nov-06	3101	Vanda	Statistical Analysis Plan
36,827	iloperidone tablets	n/a	21-Nov-06	3101	Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	13-Nov-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	251	12-Nov-06	3101	Vanda	Briefing Book
36,827	iloperidone tablets	n/a	9-Nov-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	250	18-Oct-06	3101	Vanda	Briefing Book
36,827	iloperidone tablets	n/a	13-Oct-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	249	4-Oct-06		Vanda	meeting request
36,827	iloperidone tablets	248	4-Oct-06		Vanda	meeting request
36,827	iloperidone tablets	247	29-Sep-06		Vanda	Briefing Book

36,827	iloperidone tablets	246	26-Sep-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	20-Sep-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	15-Sep-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	8-Sep-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	245	11-Aug-06	VYV683-3101	Vanda	Protocol Amendment
	iloperidone tablets	n/a	8-Aug-06		Vanda	FDA Correspondance
36,827	iloperidone tablets	244	4-Aug-06		Vanda	Briefing book
36,827	iloperidone tablets	243	27-Jul-06		Vanda	Annual Report
36,827	iloperidone tablets	242	19-Jul-06	VYV683-3101	Vanda	IND Safety report
36,827	iloperidone tablets	n/a	13-Jul-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	12-Jul-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	241	11-Jul-06		Vanda	Briefing book
36,827	iloperidone tablets	240	7-Jul-06	VYV683-3101	Vanda	IND Safety report
36,827	iloperidone tablets	239	27-Jun-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	1-Jul-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	30-Jun-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	28-Jun-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	28-Jun-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	238	21-Jun-06	VYV683-3101	Vanda	New Investigator
36,827	iloperidone tablets	237	6-Jun-06		Vanda	Briefing Book

36,827	iloperidone tablets	236	1-Jun-06	VYV683-3101	Vanda	IND Safety report
36,827	iloperidone tablets	n/a	26-May-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	235	18-May-06	VYV683-3101	Vanda	IND Safety report
36,827	iloperidone tablets	n/a	17-May-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	234	15-May-06	VYV683-3101	Vanda	New Investigator
36,827	iloperidone tablets	n/a	4-May-05		Vanda	FDA Correspondence
36,827	iloperidone tablets	233	2-May-06	VYV683-3101	Vanda	meeting request
36,827	iloperidone tablets	332	28-Apr-06	VYV683-3101	Vanda	Safety Report
36,827	iloperidone tablets	n/a	26-Apr-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	26-Apr-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	21-Apr-06	VYV683-3101	Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	21-Apr-06	VYV683-3101	Vanda	Safety Report
36,827	iloperidone tablets	n/a	21-Apr-06	VYV683-3101	Vanda	Safety Report
36,827	iloperidone tablets	n/a	20-Apr-06		Vanda	FDA Correspondence
36,827	iloperidone tablets	331	12-Apr-06		Vanda	meeting request
36,827	iloperidone tablets	232	Serial number not used - refer to Serial 332			
36,827	iloperidone tablets	231	Serial number not used - refer to Serial 331			
36,827	iloperidone tablets	230	12-Apr-06	VYV683-3101	Vanda	New Investigator
36,827	iloperidone tablets	229	10-Mar-06	VYV683-3101	Vanda	New Investigator
36,827	iloperidone tablets	228	26-Jan-06	VYV683-3101	Vanda	New Investigator

36,827	iloperidone tablets	227	6-Dec-05	VYV683-3101	Vanda	New Investigator
36,827	iloperidone tablets	226	22-Nov-05	VYV683-3101	Vanda	New Investigator
36,827	iloperidone tablets	n/a	25-Oct-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	n/a	22-Sep-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	225	20-Sep-05	VYV683-3101	Vanda	New Protocol
36,827	iloperidone tablets	n/a	9-Sep-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	n/a	8-Sep-05		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	8-Sep-05		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	12-Aug-05		Vanda	FDA Correspondence
36,827	iloperidone tablets	224	12-Aug-05		Vanda	Briefing Book
36,827	iloperidone tablets	n/a	27-Jul-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	223	28-Jun-05		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	26-Jul-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	n/a	26-Jul-05		Vanda	FDA Correspondance

36,827	iloperidone tablets	222	23-Jun-05		Vanda	Annual Report
36,827	iloperidone tablets	n/a	26-May-05		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	17-May-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	n/a	10-May-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	221	30-Mar-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	220	30-Mar-05		Vanda	FDA Correspondance
36,827	iloperidone tablets	219	13-Apr-05		Vanda	CMC
36,827	iloperidone tablets	218	30-Mar-05	VYV683-1001	Vanda	New Investigator
36,827	iloperidone tablets	217	30-Mar-05		Vanda	Briefing Book
36,827	iloperidone tablets	216	17-Feb-05	VYV683-1001	Vanda	New protocol
36,827	iloperidone tablets	215	17-Feb-05		Vanda	meeting request
36,827	iloperidone tablets	214	13-Jul-04		Vanda	FDA Correspondance
36,827	iloperidone tablets	n/a	8-Jul-04		Vanda	FDA Correspondence
36,827	iloperidone tablets	n/a	8-Jul-04		Vanda	FDA Correspondence
36,827	iloperidone tablets	213	8-Jul-04		Novartis	General Correspondance
36,827	iloperidone tablets	212	8-Jul-04		Vanda	FDA Correspondence
36,827	iloperidone tablets	211	6-Jul-04		Novartis	FDA Correspondence
36,827	iloperidone tablets	210	26-Sep-03		Novartis	Annual Report
36,827	iloperidone tablets	n/a	7-Nov-02		Novartis	FDA Correspondance
36,827	iloperidone tablets	209	18-Oct-02		Novartis	Briefing Book

36,827	iloperidone tablets	207	23-Aug-02		Novartis	Request for Meeting
36,827	iloperidone tablets	208	22-Aug-02		Novartis	Request for Meeting
36,827	iloperidone tablets	206	1-Aug-02		Novartis	Annual Report
36,827	iloperidone tablets	n/a	25-Apr-02		Novartis	FDA Correspondence
36,827	iloperidone tablets	n/a	3-Apr-02		Novartis	FDA Correspondence
36,827	iloperidone tablets	205	1-Apr-02		Novartis	New Investigator
36,827	iloperidone tablets	204	21-Mar-02		Novartis	New Investigator
36,827	iloperidone tablets	203	27-Feb-02	109	Novartis	New Protocol
36,827	iloperidone tablets	202	19-Feb-02		Novartis	Preclinical
36,827	iloperidone tablets	201	19-Feb-02	2328	Novartis	New Investigator
36,827	iloperidone tablets	200	9-Jan-02	2328	Novartis	New Investigator
36,827	iloperidone tablets	199	4-Nov-01	2328	Novartis	New Protocol
36,827	iloperidone tablets	n/a	1-Nov-01		Novartis	FDA/Novartis Meeting
36,827	iloperidone tablets	198	26-Oct-01		Novartis	General Correspondance
36,827	iloperidone tablets	n/a	24-Oct-01		Novartis	FDA Correspondence
36,827	iloperidone tablets	n/a	24-Oct-01		Novartis	FDA Correspondence
36,827	iloperidone tablets	197	11-Oct-01		Novartis	Briefing Book
36,827	iloperidone tablets	196	28-Sep-01		Novartis	Annual Report
36,827	iloperidone tablets	195	25-Sep-01		Novartis	Annual Report
36,827	iloperidone tablets	194	11-Jul-01	ILP3000	Novartis	New Investigator

36,827	iloperidone tablets	193	14-Jun-01		Novartis	Briefing Book
36,827	iloperidone tablets	n/a	11-May-01		Novartis	FDA Correspondance
36,827	iloperidone tablets	192	27-Apr-01	ILP3005	Novartis	Change to Protocol
36,827	iloperidone tablets	191	26-Apr-01		Novartis	Briefing Book
36,827	iloperidone tablets	n/a	12-Apr-01		Novartis	FDA Correspondence
36,827	iloperidone tablets	190	3-Apr-01		Novartis	CMC Amendment
36,827	iloperidone tablets	189	2-Mar-01	ILP3005	Novartis	Change to Protocol
36,827	iloperidone tablets	188	1-Mar-01		Novartis	CMC Amendment
36,827	iloperidone tablets	n/a	27-Feb-01		Novartis	FDA Correspondance
36,827	iloperidone tablets	187	23-Feb-01	ILP3005	Novartis	New Investigator
36,827	iloperidone tablets	n/a	23-Feb-01		Novartis	FDA Correspondence
36,827	iloperidone tablets	n/a	23-Feb-01		Novartis	FDA Correspondence
36,827	iloperidone tablets	186	12-Feb-01		Novartis	FDA Correspondance
36,827	iloperidone tablets	n/a	29-Jan-01		Novartis	FDA Correspondence
36,827	iloperidone tablets	185	23-Jan-01		Novartis	FDA Correspondance
36,827	iloperidone tablets	184	15-Jan-01	CILO522 0108	Novartis	New Protocol
36,827	iloperidone tablets	183	21-Dec-00		Novartis	Request for Meeting
36,827	iloperidone tablets	182	27-Nov-00		Novartis	Briefing Book
36,827	iloperidone tablets	n/a	16-Nov-00	CILO522 0112	Novartis	FDA Correspondence
36,827	iloperidone tablets	181	1-Nov-00	ILP3005	Novartis	New Investigator

36,827	iloperidone tablets	180	1-Nov-00	CILO522 2301	Novartis	CMC Amendment New Protocol
36,827	iloperidone tablets	179	23-Oct-00		Novartis	Preclinical
36,827	iloperidone tablets	178	13-Oct-00		Novartis	Request for Meeting
36,827	iloperidone tablets	n/a	10-Oct-00		Novartis	FDA Correspondence
36,827	iloperidone tablets	177	9-Oct-00	ILP3005	Novartis	Change to Protocol
36,827	iloperidone tablets	n/a	5-Oct-00		Novartis	FDA Correspondence
36,827	iloperidone tablets	176	4-Oct-00		Novartis	Clinical Information Amendment
36,827	iloperidone tablets	n/a	21-Sep-00	ILP3005	Novartis	FDA Correspondence
36,827	iloperidone tablets	175	11-Sep-00	CILO522 0105	Novartis	New Protocol Change to Protocol
36,827	iloperidone tablets	174	8-Sep-00	ILP3002	Novartis	Safety Report
36,827	iloperidone tablets	173	2-Aug-00	ILP3005	Novartis	New Investigator
36,827	iloperidone tablets	172	20-Jul-00	ILP3004	Novartis	New Protocol
36,827	iloperidone tablets	171	10-Jul-00	ILP3005	Novartis	New Investigator
36,827	iloperidone tablets	170	2-Jun-00	ILP3005	Novartis	New Investigator
36,827	iloperidone tablets	169	25-May-00	CILO522A 0107	Novartis	New Protocol New Investigator
36,827	iloperidone tablets	168	4-May-00	CILO522 0112	Novartis	Change to Protocol New Investigator
36,827	iloperidone tablets	n/a	27-Apr-00		Novartis	FDA Correspondence
36,827	iloperidone tablets	167	24-Apr-00	ILP3005	Novartis	New Investigator

36,827	iloperidone tablets	166	21-Apr-00	ILP3002	Novartis	Safety Report
36,827	iloperidone tablets	165	11-Apr-00	ILP3005/ ILP3007	Novartis	New Investigator
36,827	iloperidone tablets	164	7-Apr-00		Novartis	FDA Correspondance
36,827	iloperidone tablets	163	30-Mar-00	CILO522 0112	Novartis	New Protocol
36,827	iloperidone tablets	162	24-Mar-00	ILP3004/ ILP3005	Novartis	New Protocol New Investigator Change to Protocol
36,827	iloperidone tablets	n/a	17-Mar-00		Novartis	FDA Correspondence
36,827	iloperidone tablets	161	28-Feb-00	ILP3007	Novartis	New Investigator
36,827	iloperidone tablets	160	Serial number not used			
36,827	iloperidone tablets	159	24-Jan-00	ILP3004/ ILP3007	Novartis	New Investigator
36,827	iloperidone tablets	158	23-Dec-99	ILP3004/ ILP3007	Novartis	New Investigator
36,827	iloperidone tablets	n/a	21-Dec-99		Novartis	FDA Correspondence
36,827	iloperidone tablets	n/a	21-Dec-99		Novartis	FDA Correspondence
36,827	iloperidone tablets	157	16-Dec-99		Novartis	Request for Meeting
36,827	iloperidone tablets	156	19-Nov-99	ILP3004/ ILP3007	Novartis	New Investigator
36,827	iloperidone tablets	155	18-Nov-99		Novartis	CMC Amendment
36,827	iloperidone tablets	154	11-Nov-99		Novartis	Safety Report
36,827	iloperidone tablets	153	4-Nov-99		Novartis	FDA Correspondance
36,827	iloperidone tablets	152	18-Oct-99	ILO3004	Novartis	New Investigator
36,827	iloperidone tablets	151	13-Oct-99		Novartis	Safety Report

36,827	iloperidone tablets	150	27-Sep-99		Novartis	Safety Report
36,827	iloperidone tablets	149	23-Sep-99	ILP3007	Novartis	New Investigator
36,827	iloperidone tablets	148	23-Sep-99	ILP3003	Novartis	New Protocol
36,827	iloperidone tablets	147	21-Sep-99	ILP3004	Novartis	New Investigator
36,827	iloperidone tablets	n/a	20-Sep-99		Novartis	FDA Correspondence
36,827	iloperidone tablets	146	2-Sep-99	ILP3000	Novartis	FDA Correspondence
36,827	iloperidone tablets	145	2-Sep-99		Novartis	Annual Report
36,827	iloperidone tablets	144	2-Sep-99	ILP3007	Novartis	Change to Protocol
36,827	iloperidone tablets	143	25-Aug-99	ILP3004	Novartis	New Investigator
36,827	iloperidone tablets	142	23-Aug-99		Novartis	Safety Report
36,827	iloperidone tablets	141	16-Aug-99		Novartis	Request for FDA Guidance
36,827	iloperidone tablets	140	12-Aug-99		Novartis	Safety Report
36,827	iloperidone tablets	139	12-Aug-99	CILO522 0110	Novartis	Change to Protocol
36,827	iloperidone tablets	138	4-Aug-99		Novartis	Safety Report
36,827	iloperidone tablets	137	2-Aug-99		Novartis	CMC Amendment
36,827	iloperidone tablets	n/a	30-Jul-99		Novartis	FDA Correspondence
36,827	iloperidone tablets	136	29-Jul-99	ILP3004/ ILP3007	Novartis	New Investigator
36,827	iloperidone tablets	135	29-Jul-99	ILP3000	Novartis	Change to Protocol
36,827	iloperidone tablets	134	15-Jul-99	ILP3007	Novartis	New Protocol
36,827	iloperidone tablets	133	14-Jul-99	CILO522 0110	Novartis	New Investigator

36,827	iloperidone tablets	132	2-Jul-99	CILO522 0110	Novartis	New Protocol
36,827	iloperidone tablets	131	2-Jul-99	ILP3004	Novartis	New Investigator
36,827	iloperidone tablets	130	1-Jul-99		Novartis	CMC Amendment
36,827	iloperidone tablets	129	22-Jun-99	ILP3004/ ILP3005	Novartis	Request for Meeting
36,827	iloperidone tablets	128	9-Jun-99	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	127	7-Jun-99	ILP2001	Novartis	New Protocol
36,827	iloperidone tablets	127	7-Jun-99	ILP3007	Novartis	New Protocol
36,827	iloperidone tablets	127	7-Jun-99	ILP3000	Novartis	New Protocol
36,827	iloperidone tablets	127	7-Jun-99	ILP3004	Novartis	New Protocol
36,827	iloperidone tablets	126	2-Jun-99	ILP3001	Novartis	New Investigator
36,827	iloperidone tablets	126	2-Jun-99	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	126	2-Jun-99	ILP3001	Novartis	New Investigator
36,827	iloperidone tablets	125	12-May-99		Novartis	CMC Amendment
36,827	iloperidone tablets	124	11-May-99		Novartis	CMC Amendment
36,827	iloperidone tablets	124	11-May-99		Novartis	CMC Amendment
36,827	iloperidone tablets	123	26-Apr-99		Novartis	Preclinical
36,827	iloperidone tablets	122	31-Mar-99		Novartis	FDA correspondence
36,827	iloperidone tablets	121	20-Apr-99		Novartis	FDA Correspondence
36,827	iloperidone tablets	120	13-Apr-99	ILP3007	Novartis	New Protocol New Investigator
36,827	iloperidone tablets	119	2-Apr-99		Novartis	New Investigator

36,827	iloperidone tablets	118	1-Apr-99	ILP3000/ ILP3004	Novartis	Request for FDA Guidance
36,827	iloperidone tablets	117	24-Mar-99	ILP3000	Novartis	Change to Protocol
36,827	iloperidone tablets	116	17-Mar-99	ILP3000	Novartis	Safety Report
36,827	iloperidone tablets	n/a	9-Mar-99		Novartis	CMC Amendment
36,827	iloperidone tablets	115	3-Mar-99	ILP3004	Novartis	New Protocol
36,827	iloperidone tablets	114	19-Feb-99	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	113	15-Feb-99		Novartis	Other
36,827	iloperidone tablets	112	15-Feb-99	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	111	12-Feb-99		Novartis	Annual Report
36,827	iloperidone tablets	n/a	10-Feb-99		Novartis	FDA/Novartis Meeting Request for FDA comments
36,827	iloperidone tablets	110	4-Feb-99	ILP2001	Novartis	Change to Protocol
36,827	iloperidone tablets	n/a	3-Feb-99		Novartis	Briefing Book
36,827	iloperidone tablets	109	29-Jan-99		Novartis	CMC Amendment
36,827	iloperidone tablets	108	18-Jan-99	ILO522 0103	Novartis	New Protocol New Investigator
36,827	iloperidone tablets	107	8-Jan-99		Novartis	Request for FDA Guidance Request for FDA Meeting
36,827	iloperidone tablets	106	7-Jan-99	ILP3000	Novartis	Change to Protocol
36,827	iloperidone tablets	106	7-Jan-99	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator

36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3001	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator

36,827	iloperidone tablets	105	8-Dec-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	104	30-Nov-98		Novartis	FDA Correspondence
36,827	iloperidone tablets	103	24-Nov-98	ILO522 0102	Novartis	New Protocol New Investigator
36,827	iloperidone tablets	n/a	19-Nov-98		Novartis	FDA Correspondence
36,827	iloperidone tablets	102	9-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	102	9-Nov-98	ILP3000	Novartis	Change to Protocol New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	101	3-Nov-98	ILP2001	Novartis	Change to Protocol
36,827	iloperidone tablets	n/a	22-Oct-98	ILP2001	Novartis	Clinical Information Amendment
36,827	iloperidone tablets	100	21-Oct-98	ILP2001	Novartis	Change to Protocol

36,827	iloperidone tablets	99	21-Oct-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	98	14-Oct-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	98	14-Oct-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	97	13-Oct-98		Novartis	CMC Amendment
36,827	iloperidone tablets	96	24-Sep-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	96	24-Sep-98	ILP3000	Novartis	New Protocol New Investigator
36,827	iloperidone tablets	96	24-Sep-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	96	24-Sep-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	96	24-Sep-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	96	24-Sep-98	ILP3000	Novartis	New Investigator
36,827	iloperidone tablets	95	21-Sep-98	CILO522 0104	Novartis	New Protocol New Investigator
36,827	iloperidone tablets	n/a	17-Sep-98	CILO522 0104	Novartis	Request for FDA Meeting
36,827	iloperidone tablets	n/a	14-Sep-98		Novartis	Request for FDA Meeting Briefing Book
36,827	iloperidone tablets	94	14-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	94	14-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator

36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	93	2-Sep-98	ILP2001	Novartis	New Investigator
36,827	iloperidone tablets	92	5-Aug-98		Novartis	CMC Amendment
36,827	iloperidone tablets	91	17-Jun-98	ILP2001	Novartis	New Protocol
36,827	iloperidone tablets	n/a	16-Jun-98		Novartis	FDA Correspondence
36,827	iloperidone tablets	90	Serial number not used			
36,827	iloperidone tablets	89	5-Dec-97		Novartis	FDA Correspondence
36,827	iloperidone tablets	88	1-Nov-97		Titan	FDA Correspondence
36,827	iloperidone tablets	87	23-Sep-97	300	Titan	New Investigator
36,827	iloperidone tablets	87	23-Sep-97	300	Titan	New Investigator
36,827	iloperidone tablets	87	23-Sep-97	300	Titan	New Protocol New Investigator
36,827	iloperidone tablets	87	23-Sep-97	300	Titan	New Investigator
36,827	iloperidone tablets	87	23-Sep-97	300	Titan	New Investigator
36,827	iloperidone tablets	87	23-Sep-97	300	Titan	New Investigator
36,827	iloperidone tablets	87	23-Sep-97	300	Titan	New Investigator
36,827	iloperidone tablets	86	12-Sep-97	105/ 106	Titan	Clinical Study Reports CMC Amendment Preclinical

36,827	iloperidone tablets	85	23-Jun-97		Titan	Annual Report
36,827	iloperidone tablets	84	4-Jun-97		Titan	Precinical
36,827	iloperidone tablets	n/a	14-Mar-97		Titan	FDA Correspondence
36,827	iloperidone tablets	83	4-Mar-97		Titan	CMC Amendment
36,827	iloperidone tablets	82	13-Feb-97		Titan	FDA Correspondence
36,827	iloperidone tablets	81	2-Feb-97		HMR	FDA Correspondence
36,827	iloperidone tablets	80	15-Nov-96	201/ 202/ 203	HMR	New Investigator
36,827	iloperidone tablets	79	24-Oct-96		HMR	Preclinical/ FDA Correspondence
36,827	iloperidone tablets	n/a	9-Sep-96		HMR	Preclinical/ FDA Correspondence
36,827	iloperidone tablets	78	6-Sep-96		HMR	Preclinical/ FDA Correspondence
36,827	iloperidone tablets	77	31-Jul-96		HMR	Annual Report
36,827	iloperidone tablets	76	21-May-96	201/ 205/ 3003	HMR	New Investigator
36,827	iloperidone tablets	75	17-Apr-96	3003	HMR	New Investigator
36,827	iloperidone tablets	74	1-Apr-96		HMR	CMC Amendment
36,827	iloperidone tablets	73	28-Mar-96	3003	HMR	New Investigator
36,827	iloperidone tablets	72	28-Mar-96		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	20-Mar-96		HMR	CMC Amendment
36,827	iloperidone tablets	n/a	15-Mar-96		HMR	CMC Amendment
36,827	iloperidone tablets	n/a	29-Feb-96		HMR	CMC Amendment
36,827	iloperidone tablets	71	23-Feb-96	3003	HMR	New Investigator

36,827	iloperidone tablets	n/a	23-Feb-96		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	23-Feb-96		HMR	CMC Amendment
36,827	iloperidone tablets	n/a	22-Feb-96		HMR	CMC Amendment
36,827	iloperidone tablets	n/a	21-Feb-96		HMR	CMC Amendment
36,827	iloperidone tablets	70	16-Feb-96		HMR	CMC Amendment
36,827	iloperidone tablets	69	12-Feb-96		HMR	Preclinical
36,827	iloperidone tablets	68	9-Feb-96		HMR	FDA Correspondence
36,827	iloperidone tablets	67	15-Jan-96		HMR	CMC Amendment
36,827	iloperidone tablets	66	5-Jan-96	3003	HMR	New Protocol
36,827	iloperidone tablets	n/a	20-Nov-95		HMR	FDA Correspondence
36,827	iloperidone tablets	65	17-Nov-95	203	HMR	Change to Protocol
36,827	iloperidone tablets	64	17-Nov-95		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	1-Nov-95		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	23-Oct-95		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	20-Oct-95		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	13-Oct-95		HMR	FDA Correspondence
36,827	iloperidone tablets	63	9-Oct-95		HMR	Briefing Book
36,827	iloperidone tablets	62	2-Oct-95		HMR	Briefing Book
36,827	iloperidone tablets	n/a	27-Sep-95		HMR	FDA Correspondence
36,827	iloperidone tablets	61	20-Sep-95		HMR	CMC Amendment

36,827	iloperidone tablets	60	29-Aug-95	106	HMR	New Protocol New Investigator
36,827	iloperidone tablets	59	22-Aug-95	203	HMR	New Protocol New Investigator
36,827	iloperidone tablets	n/a	17-Aug-95		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	11-Aug-95		HMR	FDA Correspondence
36,827	iloperidone tablets	58	4-Aug-95		HMR	CMC Amendment
36,827	iloperidone tablets	57	4-Aug-95		HMR	Briefing Book
36,827	iloperidone tablets	56	31-Jul-95		HMR	Preclinical
36,827	iloperidone tablets	55	6-Sep-95		HMR	Annual Report
36,827	iloperidone tablets	54	27-Jul-95		HMR	Preclinical
36,827	iloperidone tablets	53	27-Jul-95	202/ 200/ 199	HMR	Clinical Study Reports
36,827	iloperidone tablets	52	5-Jul-95		HMR	CMC Amendment
36,827	iloperidone tablets	n/a	24-Apr-95		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	27-Mar-95	202	HMR	FDA Correspondence
36,827	iloperidone tablets	51	14-Mar-95	201	HMR	Change to Protocol New Investigator
36,827	iloperidone tablets	50	10-Mar-95		HMR	Safety Report
36,827	iloperidone tablets	49	10-Mar-95		HMR	Preclinical
36,827	iloperidone tablets	n/a	24-Feb-95	105	HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	17-Jan-95	105	HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	16-Jan-95	105	HMR	FDA Correspondence

36,827	iloperidone tablets	48	5-Jan-95	201	HMR	New Investigator
36,827	iloperidone tablets	n/a	22-Dec-94		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	20-Dec-94	105	HMR	FDA Correspondence
36,827	iloperidone tablets	47	8-Dec-94	202	HMR	Change to Protocol
36,827	iloperidone tablets	46	7-Dec-94		HMR	Safety Report
36,827	iloperidone tablets	45	11-Nov-94	201	HMR	New Investigator
36,827	iloperidone tablets	n/a	4-Nov-94		HMR	FDA Correspondence
36,827	iloperidone tablets	44	27-Oct-94	205	HMR	New Protocol New Investigator
36,827	iloperidone tablets	43	23-Aug-94		HMR	Preclinical
36,827	iloperidone tablets	n/a	28-Jul-94		HMR	Preclinical/ FDA Correspondence
36,827	iloperidone tablets	42	27-Jul-94	201/ 202	HMR	New Investigator
36,827	iloperidone tablets	n/a	20-Jul-94		HMR	FDA Correspondence
36,827	iloperidone tablets	41	12-Jun-94	201/ 202	HMR	New Investigator
36,827	iloperidone tablets	40	11-Jul-94		HMR	Preclinical
36,827	iloperidone tablets	39	20-Jul-94		HMR	Annual Report
36,827	iloperidone tablets	n/a	20-Jun-94		HMR	FDA Correspondence
36,827	iloperidone tablets	38	6-Jun-94	202	HMR	New Investigator
36,827	iloperidone tablets	38	6-Jun-94	201	HMR	Change to Protocol New Investigator
36,827	iloperidone tablets	37	27-Jun-94		HMR	Annual Report

36,827	iloperidone tablets	36	26-May-94	202	HMR	New Investigator
36,827	iloperidone tablets	35	17-May-94		HMR	Preclinical
36,827	iloperidone tablets	n/a	25-Apr-94		HMR	FDA Correspondence
36,827	iloperidone tablets	34	16-Mar-94	202	HMR	New Investigator
36,827	iloperidone tablets	33	22-Jan-94	202	HMR	New Investigator
36,827	iloperidone tablets	32	7-Dec-93	202	HMR	New Investigator
36,827	iloperidone tablets	31	1-Nov-93	201	HMR	Change to Protocol New Investigator
36,827	iloperidone tablets	30	22-Oct-93	202	HMR	New Investigator
36,827	iloperidone tablets	n/a	28-Sep-93		HMR	FDA Correspondence
36,827	iloperidone tablets	29	31-Aug-93	202	HMR	Change to Protocol New Investigator
36,827	iloperidone tablets	28	19-Aug-93	201	HMR	Change to Protocol
36,827	iloperidone tablets	27	17-Aug-93	202	HMR	New Investigator
36,827	iloperidone tablets	26	4-Aug-93	199	HMR	Change to Protocol
36,827	iloperidone tablets	n/a	2-Aug-93		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	22-Jul-93		HMR	FDA Correspondence
36,827	iloperidone tablets	25	12-Jul-93	202	HMR	New Investigator
36,827	iloperidone tablets	n/a	9-Jul-93		HMR	FDA Correspondence
36,827	iloperidone tablets	24	18-Jun-93	201	HMR	New Investigator
36,827	iloperidone tablets	n/a	16-Jun-93		HMR	FDA Correspondence

36,827	iloperidone tablets	23	14-Jun-93		HMR	Annual Report
36,827	iloperidone tablets	22	9-Jun-93		HMR	Annual Report
36,827	iloperidone tablets	21	18-May-93		HMR	Preclinical
36,827	iloperidone tablets	20	18-May-93	101	HMR	Clinical Study Report
36,827	iloperidone tablets	19	11-May-93	202	HMR	New Protocol
36,827	iloperidone tablets	n/a	20-Apr-93		HMR	FDA Correspondence
36,827	iloperidone tablets	18	25-Mar-93		HMR	CMC Amendment
36,827	iloperidone tablets	17	25-Mar-93	103	HMR	Clinical Study Report
36,827	iloperidone tablets	16	8-Mar-93		HMR	Safety Report
36,827	iloperidone tablets	15	16-Feb-93	201	HMR	New Protocol New Investigator
36,827	iloperidone tablets	14	14-Jan-93	199/ 200	HMR	Change to Protocol
36,827	iloperidone tablets	13	30-Dec-92		HMR	Preclinical
36,827	iloperidone tablets	12	1-Dec-92	200	HMR	Change to Protocol
36,827	iloperidone tablets	11	17-Nov-92		HMR	Safety Report
36,827	iloperidone tablets	10	15-Oct-92		HMR	CMC Amendment
36,827	iloperidone tablets	n/a	1-Sep-92		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	27-Aug-92		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	26-Aug-92		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	25-Aug-92		HMR	FDA Correspondence
36,827	iloperidone tablets	9	14-Aug-92	199	HMR	New Protocol New Investigator

36,827	iloperidone tablets	8	4-Aug-92		HMR	CMC Amendment
36,827	iloperidone tablets	7	4-Aug-92		HMR	Request for FDA Meeting
36,827	iloperidone tablets	6	1-Jul-92		HMR	Annual Report
36,827	iloperidone tablets	5	3-Jun-92		HMR	Safety Report
36,827	iloperidone tablets	n/a	8-May-92		HMR	FDA Correspondence
36,827	iloperidone tablets	4	9-Mar-92	200	HMR	New Protocol New Investigator
36,827	iloperidone tablets	n/a	24-Feb-92	103	HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	17-Jan-92		HMR	FDA Correspondence
36,827	iloperidone tablets	3	26-Dec-91	103	HMR	New Protocol New Investigator
36,827	iloperidone tablets	2	21-Oct-91	101	HMR	Change to Protocol
36,827	iloperidone tablets	1	4-Sep-91		HMR	Preclinical
36,827	iloperidone tablets	n/a	14-Aug-91		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	6-Jun-91		HMR	FDA Correspondence
36,827	iloperidone tablets	n/a	3-May-91		HMR	FDA Correspondence
36,827	iloperidone tablets	0	25-Apr-91		HMR	Original IND Submission
36,827	iloperidone tablets	0	25-Apr-91		HMR	Original IND Submission

EXHIBIT 11

NDA#	Product Name	Submission No	Submission Date	Description	Sponsor
22-192	iloperidone tablets	0022	14-May-09	SPL Label	Vanda
22-192	iloperidone tablets	0021	12-May-09	Patent Information - FDA Form 3542	Vanda
22-192	iloperidone tablets	0020	17-Mar-09	Updated graphics for carton and container labels based on second round of review by DMEPA	Vanda
22-192	iloperidone tablets	0019	10-Mar-09	Updated graphics for carton and container labels based on review by DMEPA	Vanda
22-192	iloperidone tablets	0018	9-Jan-09	Change of primary contact to Dr. John Feeney	Vanda
22-192	iloperidone tablets	0017	19-Nov-08	Resubmission of information for Tradename Review	Vanda
22-192	iloperidone tablets	0016	6-Nov-08	Submission of the Complete Response	Vanda
22-192	iloperidone tablets	0015	28-Aug-08	Amendment to Briefing Book for September 10, 2008, meeting with the FDA	Vanda
22-192	iloperidone tablets	0014	21-Aug-08	Briefing Book for September 10, 2008, meeting with the FDA	Vanda
22-192	iloperidone tablets	0013	4-Aug-08	Letters informing of Intent to File and amendment and requesting a meeting	Vanda
22-192	iloperidone tablets	0012	8-Jul-08	Request for Review of Tradenames to DMETS	Vanda
22-192	iloperidone tablets	0011	20-Jun-08	CMC validated methods update	Vanda
22-192	iloperidone tablets	0010	13-Jun-08	CMC validated methods update	Vanda
22-192	iloperidone tablets	0009	16-May-08	SAE/AE narratives request, AE thesaurus, ILP3005 CNTF data, additional CMC responses to the April 2, 2008 inquiry	Vanda
22-192	iloperidone tablets	0008	1-May-08	ILO522 0108 CSR Amendment 2	Vanda

22-192	iloperidone tablets	0007	25-Apr-08	Submission of Vanda's responses to the April 2, 2008 CMC inquiry	Vanda
22-192	iloperidone tablets	0006	18-Apr-08	Final graphics of sample packs, bottles and cartons, updated SAE and AE tables and updated package insert	Vanda
22-192	iloperidone tablets	0005	17-Mar-08	Tablet stability data, updated draft package insert and PK bioanalytical QC data	Vanda
22-192	iloperidone tablets	0004	20-Feb-08	Bioanalytical PK reports and PK storage summary table	Vanda
22-192	iloperidone tablets	0003	23-Jan-08	Additional ISS Tables requested by the FDA in the Day 60 filing communication, 3101 OLE CSR, 3101 ST CSR amendment, 3101-PG2 CSR, updated financial disclosures, 120-day safety update	Vanda
22-192	iloperidone tablets	0002	14-Dec-07	PK Datasets requested by Division for QT Study Report, Study No: ILO522 2328	Vanda
22-192	iloperidone tablets	0001	26-Nov-07	Pharmacology Information requested by Division	Vanda
22-192	iloperidone tablets	0000	27-Sep-07	Submission of NDA	Vanda

NDA#	Product Name	Communication Type	Communication Date	Description
22-192	iloperidone tablets	Email	6-May-09	Vanda receives FDA approval letter
22-192	iloperidone tablets	Email	6-May-09	Vanda receives final agreed upon labeling
22-192	iloperidone tablets	Email	5-May-09	Vanda responds to FDA's proposed labeling chages
22-192	iloperidone tablets	Email	5-May-09	FDA sends proposed labeling changes
22-192	iloperidone tablets	Email	1-May-09	Vanda sends FDA additional labeling changes
22-192	iloperidone tablets	Email	30-Apr-09	FDA verifies action date
22-192	iloperidone tablets	Telephone Call	28-Apr-09	FDA provides Vanda review status update
22-192	iloperidone tablets	Email	27-Apr-09	Vanda requests review status update from FDA
22-192	iloperidone tablets	Email	24-Apr-09	Vanda provides FDA with P95 Carc study dates
22-192	iloperidone tablets	Email	24-Apr-09	FDA requests confirmation of P95 Carc study dates
22-192	iloperidone tablets	Email	15-Apr-09	Vanda provides FDA with requested dates for post-marketing requirements
22-192	iloperidone tablets	Email	15-Apr-09	FDA requests additional dates for post-marketing requirements
22-192	iloperidone tablets	Email	9-Apr-09	Vanda sends FDA additional labeling changes
22-192	iloperidone tablets	Email	3-Apr-09	Vanda sends FDA additional labeling changes
22-192	iloperidone tablets	Email	31-Mar-09	Vanda requests review status update from FDA
22-192	iloperidone tablets	Email	30-Mar-09	Vanda provides FDA latest label with tracked changes
22-192	iloperidone tablets	Email	30-Mar-09	FDA requests lastest label with tracked changes
22-192	iloperidone tablets	Email	23-Mar-09	Vanda agrees with post-marketing requirement
22-192	iloperidone tablets	Email	23-Mar-09	FDA proposes a post-marketing requirement

22-192	iloperidone tablets	Email	23-Mar-09	DMEPA informs Vanda that their review of packagine is complete
22-192	iloperidone tablets	Email	23-Mar-09	Vanda agrees with proposed labeling changes
22-192	iloperidone tablets	Email	23-Mar-09	Vanda agrees with post-marketing requirements
22-192	iloperidone tablets	Email	23-Mar-09	FDA proposes post-marketing requirements
22-192	iloperidone tablets	Email	23-Mar-09	FDA proposes labeling changes
22-192	iloperidone tablets	Email	18-Mar-09	FDA agrees to Vanda's proposed labeling language
22-192	iloperidone tablets	Email	17-Mar-09	Vanda submits updated packaging graphics to DMEPA
22-192	iloperidone tablets	Email	16-Mar-09	DMEPA requests changes to packaging graphics
22-192	iloperidone tablets	Email	16-Mar-09	Vanda sends FDA with proposed labeling changes
22-192	iloperidone tablets	Email	16-Mar-09	DMEPA verifies titration card language
22-192	iloperidone tablets	Telephone Call	16-Mar-09	Teleconference with DMEPA regarding packaging graphics
22-192	iloperidone tablets	Email	11-Mar-09	FDA accepts Vanda proposed labeling language
22-192	iloperidone tablets	Email	10-Mar-09	Vanda submits updated packaging graphics to DMEPA
22-192	iloperidone tablets	email	9-Mar-09	DMEPA provides recommendations to Vanda regarding packaging graphics
22-192	iloperidone tablets	Email	6-Mar-09	Receipt of DMEPA's comments to Fanapt packaging materials
22-192	iloperidone tablets	Email	24-Feb-09	Vanda provides FDA location of data to support labeling claim
22-192	iloperidone tablets	Email	24-Feb-09	FDA requests location of data to support a labeling claim
22-192	iloperidone tablets	Email	19-Feb-09	Vanda responds to FDA's comments to Fanapt label
22-192	iloperidone tablets	Email	19-Feb-09	FDA sends Vanda comments to Fanapt label
22-192	iloperidone tablets	Email	18-Feb-09	Vanda provides FDA location of data to support labeling claim

22-192	iloperidone tablets	Email	18-Feb-09	FDA requets locatin of data to support labeling claim
22-192	iloperidone tablets	Email	13-Feb-09	FDA approves tradename FANAPT
FDA	iloperidone tablets	Telephone Call	13-Feb-09	FDA teleconference regarding NDC codes
22-192	iloperidone tablets	Email	11-Feb-09	Vanda provides FDA updated pediatric plan
22-192	iloperidone tablets	Email	11-Feb-09	FDA requests updates to pediatric plan
22-192	iloperidone tablets	Telephone Call	11-Feb-09	From: Kimberly Updegraff regarding PERC review of pediatric development plan.
22-192	iloperidone tablets	Email	10-Feb-09	Vanda provides FDA pediatric plan
22-192	iloperidone tablets	Email	10-Feb-09	FDA requests pediatric plan
22-192	iloperidone tablets	Email	3-Feb-09	Vanda provides FDA requested exposure data
22-192	iloperidone tablets	Email	3-Feb-09	FDA requets verification of exposure data
22-192	iloperidone tablets	Email	15-Jan-09	Vanda provides FDA status update for P95 carc study
22-192	iloperidone tablets	Email	15-Jan-09	FDA requests status update for P95 carc study
22-192	iloperidone tablets	Email	9-Jan-09	Vanda provides FDA change of contact information
22-192	iloperidone tablets	Email	2-Dec-08	Vanda provides DMEPA verification of tradenames to be reviewed
22-192	iloperidone tablets	Email	2-Dec-08	DMEPA requests verification of which tradenames are to be reviewed
22-192	iloperidone tablets	Email	19-Nov-08	FDA provides new PDUFA action date of May 6, 2009
22-192	iloperidone tablets	Email	19-Nov-08	Vanda queries FDA regarding status of tradename review
22-192	iloperidone tablets	Email	6-Nov-08	Vanda submits a Complete Response to FDA's July 25, 2008 action letter to the CTD
22-192	iloperidone tablets	Email	22-Sep-08	Receipt of September 10, 2008 meeting minutes
22-192	iloperidone tablets	Meeting	10-Sep-08	NDA action meeting with FDA

22-192	iloperidone tablets	Email	3-Sep-08	FDA provides pre-meeting minutes to 10-Sept-08 meeting
22-192	iloperidone tablets	Email	28-Aug-08	Vanda submits Amendment 1 to the 10-Sept-08 meeting briefing book
22-192	iloperidone tablets	Email	18-Aug-08	Vanda submits 10-Sept-08 briefing book to FDA
22-192	iloperidone tablets	Email	15-Aug-08	Vanda provides FDA with requested word document
22-192	iloperidone tablets	Email	15-Aug-08	FDA requests questions for 10-Sept-08 meeting as a stand alone word document
22-192	iloperidone tablets	Email	12-Aug-08	FDA grants NDA action meeting for 10-Sept-08
22-192	iloperidone tablets	Email	12-Aug-08	Vanda accepts possible meeting dates
22-192	iloperidone tablets	Email	12-Aug-08	FDA proposes possible meeting dates
22-192	iloperidone tablets	Email	1-Aug-08	Vanda requests meeting with FDA to discuss NDA action letter
22-192	iloperidone tablets	Email	25-Jul-08	Vanda receives FDA action letter
22-192	iloperidone tablets	Email	24-Jul-08	Vanda resubmits Form 2656 as requested
22-192	iloperidone tablets	Email	24-Jul-08	FDA confirms PDUFA action date of 25-July-08
22-192	iloperidone tablets	Email	22-Jul-08	FDA provides Vanda FEI number
22-192	iloperidone tablets	Email	8-Jul-08	Vanda requests review of new tradenames
22-192	iloperidone tablets	Email	23-Jun-08	Vanda provides additional support for proposed tradenames
22-192	iloperidone tablets	Email	23-Jun-08	Vanda submits Sequence 0011 to NDA
22-192	iloperidone tablets	Email	18-Jun-08	Vanda provides iloperidone IND number to FDA reviewer
22-192	iloperidone tablets	Email	18-Jun-08	Vanda provides updated validation reports to FDA reviewers
22-192	iloperidone tablets	Email	18-Jun-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	18-Jun-08	FDA reviewer reviewer ask questions to Vanda

22-192	iloperidone tablets	Email	13-Jun-08	Vanda submits Sequence 0011 to NDA
22-192	iloperidone tablets	Telephone Call	13-Jun-08	FDA teleconference with CMC review team
22-192	iloperidone tablets	Email	12-Jun-08	Vanda provides FDA reviewer with requested data
22-192	iloperidone tablets	Email	12-Jun-08	FDA reviewer requests additonal data
22-192	iloperidone tablets	Email	9-Jun-08	FDA confirms receipt of the WGAS data
22-192	iloperidone tablets	Email	7-Jun-08	Vanda submits WGAS data to FDA
22-192	iloperidone tablets	Email	6-Jun-08	FDA provides official review of proposed tradenames
22-192	iloperidone tablets	Email	6-Jun-08	Vanda provides FDA reviewers additional validation reports
22-192	iloperidone tablets	Email	4-Jun-08	Vanda replies to FDA reviewer's questions
22-192	iloperidone tablets	Email	4-Jun-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	2-Jun-08	Vanda replies to FDA reviewer's questions
22-192	iloperidone tablets	Telephone Call	2-Jun-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	29-May-08	FDA requests WGAS data
22-192	iloperidone tablets	Email	28-May-08	Vanda sends CNTF and CYP2D6 datasets to FDA reviewer
22-192	iloperidone tablets	Email	23-May-08	FDA reviewer requests CNTF and CYP2D6 datasets
22-192	iloperidone tablets	Email	22-May-08	FDA provides Vanda labeler code
22-192	iloperidone tablets	Email	21-May-08	FDA recommends Vanda contact CDRH to discuss possible diagnostic assays
22-192	iloperidone tablets	Email	16-May-08	Vanda submits Sequence 009 to the NDA
22-192	iloperidone tablets	Email	15-May-08	Vanda provides additional data to FDA review team
22-192	iloperidone tablets	Email	14-May-08	Vanda provides FDA data requested on 9May08

22-192	iloperidone tablets	Email	13-May-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	13-May-08	Vanda receives questions from FDA reviewer
22-192	iloperidone tablets	Email	12-May-08	FDA revises safety data request of 9-May-08
22-192	iloperidone tablets	Email	9-May-08	FDA requests additional cut to the safety data
22-192	iloperidone tablets	Telephone Call	1-May-08	FDA confirms receipt of Vanda's response to the FDA audit finding
22-192	iloperidone tablets	Email	1-May-08	Vanda submits Sequence 008 to CTD
22-192	iloperidone tablets	Hard Copy Mail	1-May-08	Vanda submits response to FDA audit finding
22-192	iloperidone tablets	Email	1-May-08	Vanda provides FDA location of data requested on 30-Apr-08 within the NDA
22-192	iloperidone tablets	Email	30-Apr-08	FDA request location of data within the NDA
22-192	iloperidone tablets	Email	25-Apr-08	Vanda submits Sequence 007 to CTD
22-192	iloperidone tablets	Telephone Call	21-Apr-08	FDA teleconference with DMETS
22-192	iloperidone tablets	Email	21-Apr-08	Vanda submits Sequence 006 to CTD
22-192	iloperidone tablets	Telephone Call	17-Apr-08	FDA teleconfence regarding audits of study centers
22-192	iloperidone tablets	Email	17-Apr-08	Vanda supplies FDA reviewer with code definitions
22-192	iloperidone tablets	Email	17-Apr-08	FDA reviwer requests code definitions
22-192	iloperidone tablets	Email	15-Apr-08	FDA informs Vanda on a clnical trial site to be audited
22-192	iloperidone tablets	Email	15-Apr-08	FDA requests draft label to be submitted in a different format
22-192	iloperidone tablets	Email	15-Apr-08	FDA provides update on tradename review
22-192	iloperidone tablets	Email	15-Apr-08	Vanda requests tradename review status update from FDA
22-192	iloperidone tablets	Email	14-Apr-08	Vanda supplies FDA reviewer with code definitions

22-192	iloperidone tablets	Email	14-Apr-08	FDA reviwer requests code definitions
22-192	iloperidone tablets	Telephone Call	11-Apr-08	FDA teleconference with DMETS
22-192	iloperidone tablets	Email	11-Apr-08	FDA provides Vanda recommendations for PLR formatting
22-192	iloperidone tablets	Email	10-Apr-08	FDA requests final packaging graphics to be submitted to NDA
22-192	iloperidone tablets	Email	10-Apr-08	Vanda supplies FDA reviewer with additional data
22-192	iloperidone tablets	Email	10-Apr-08	FDA reviewer requests additonal data
22-192	iloperidone tablets	Telephone Call	9-Apr-08	FDA confirms Vanda audit date
22-192	iloperidone tablets	Email	9-Apr-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	9-Apr-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Telephone Call	8-Apr-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	8-Apr-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	7-Apr-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	7-Apr-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	3-Apr-08	Vanda provides additional data to FDA reviewer
22-192	iloperidone tablets	Email	3-Apr-08	FDA reviewer requests additonal data
22-192	iloperidone tablets	Email	2-Apr-08	FDA communication regarding study site audits
22-192	iloperidone tablets	Email	2-Apr-08	FDA reviewer requests additonal data
22-192	iloperidone tablets	Telephone Call	2-Apr-08	FDA communication regarding study site audits
22-192	iloperidone tablets	Email	27-Mar-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	26-Mar-08	FDA reviewer sends questions to Vanda

22-192	iloperidone tablets	Email	26-Mar-08	Vanda sends FDA site auditors requested data
22-192	iloperidone tablets	Email	26-Mar-08	FDA site auditors request data from Vanda
22-192	iloperidone tablets	Email	25-Mar-08	Vanda provides additional data to FDA reviewer
22-192	iloperidone tablets	Email	25-Mar-08	FDA reviewer requests additonal data
22-192	iloperidone tablets	Email	24-Mar-08	Vanda provides location of data to FDA reviewer
22-192	iloperidone tablets	Email	24-Mar-08	FDA reviewer requests location of data
22-192	iloperidone tablets	Email	19-Mar-08	Vanda provides additional data to FDA reviewer
22-192	iloperidone tablets	Email	19-Mar-08	FDA reviewer requests additonal data
22-192	iloperidone tablets	Email	18-Mar-08	Vanda sends FDA site auditors requested data
22-192	iloperidone tablets	Email	18-Mar-08	FDA site auditors request data from Vanda
22-192	iloperidone tablets	Email	18-Mar-08	Vanda submits Sequence 005 to NDA
22-192	iloperidone tablets	Email	17-Mar-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	17-Mar-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	14-Mar-08	Vanda sends FDA site auditors requested data
22-192	iloperidone tablets	Email	14-Mar-08	FDA site auditors request data from Vanda
22-192	iloperidone tablets	Email	13-Mar-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	13-Mar-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	12-Mar-08	Vanda sends FDA site auditors requested data
22-192	iloperidone tablets	Telephone Call	12-Mar-08	FDA site auditors request data from Vanda
22-192	iloperidone tablets	Email	12-Mar-08	FDA confirms dates for study site audits

22-192	iloperidone tablets	Email	10-Mar-08	FDA confirms dates for study site audits
22-192	iloperidone tablets	Email	10-Mar-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	7-Mar-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	7-Mar-08	FDA informs Vanda of study site audits
22-192	iloperidone tablets	Email	6-Mar-08	Vanda provides FDA location of data within the CTD
22-192	iloperidone tablets	Email	6-Mar-08	FDA reviewer requests location of data within the CTD
22-192	iloperidone tablets	Email	5-Mar-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	5-Mar-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	5-Mar-08	Vanda requests meeting with FDA
22-192	iloperidone tablets	Email	3-Mar-08	FDA informs Vanda of study site audits
22-192	iloperidone tablets	Email	27-Feb-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	27-Feb-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	26-Feb-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	26-Feb-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	22-Feb-08	Vanda provides FDA location of data within the CTD
22-192	iloperidone tablets	Email	22-Feb-08	FDA reviewer request location of data within CTD
22-192	iloperidone tablets	Email	21-Feb-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	21-Feb-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	20-Feb-08	Vanda responds to FDA reviwer's questions

22-192	iloperidone tablets	Email	20-Feb-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	19-Feb-08	Vanda sends FDA prototypes of packaging material
22-192	iloperidone tablets	Email	19-Feb-08	FDA requests prototypes of packaging material
22-192	iloperidone tablets	Email	19-Feb-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	19-Feb-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	19-Feb-08	Vanda submits Sequence 004 to NDA
22-192	iloperidone tablets	Email	14-Feb-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	14-Feb-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Telephone Call	13-Feb-08	Vanda responds to FDA reviwer's questions
22-192	iloperidone tablets	Email	13-Feb-08	FDA reviewer sends questions to Vanda
22-192	iloperidone tablets	Email	8-Feb-08	FDA informs Vanda of potential study site audits
22-192	iloperidone tablets	Email	4-Feb-08	Vanda informs FDA that one of the proposed site's to be audited with the death of the PI
22-192	iloperidone tablets	Email	4-Feb-08	FDA informs Vanda of potential study site audits
22-192	iloperidone tablets	Email	1-Feb-08	Vanda provides FDA with additional data
22-192	iloperidone tablets	Telephone Call	1-Feb-08	FDA requests additional data
22-192	iloperidone tablets	Email	29-Jan-08	Vanda responds to FDA reviewer's questions
22-192	iloperidone tablets	Telephone Call	29-Jan-08	FDA review sends questions to Vanda
22-192	iloperidone tablets	Email	29-Jan-08	Vanda submits 120-day safety updated (Sequence 003) to NDA
22-192	iloperidone tablets	Email	7-Jan-08	Vanda supplies SAS codes to FDA
22-192	iloperidone tablets	Email	7-Jan-08	FDA requests SAS codes

22-192	iloperidone tablets	Email	4-Jan-08	Vanda supplies SAS codes to FDA
22-192	iloperidone tablets	Email	4-Jan-08	FDA requests SAS codes
22-192	iloperidone tablets	Email	21-Dec-07	FDA notifies Vanda of potential sites to be audited
22-192	iloperidone tablets	Email	19-Dec-07	Vanda provides location of datasets in the NDA
22-192	iloperidone tablets	Email	19-Dec-07	FDA requests location of datasets within NDA
22-192	iloperidone tablets	Email	14-Dec-07	Vanda provides FDA with additional data
22-192	iloperidone tablets	Email	14-Dec-07	FDA requets additional data
22-192	iloperidone tablets	Email	11-Dec-07	Vanda provides FDA with additional data
22-192	iloperidone tablets	Email	11-Dec-07	FDA requets additional data
22-192	iloperidone tablets	Email	26-Nov-07	FDA notification of NDA 22-192 filing
22-192	iloperidone tablets	Telephone Call	19-Nov-07	IND number used for Study 3101 confirmed
22-192	iloperidone tablets	Email	16-Nov-07	Vanda provides FDA data requested on 13-Nov-07
22-192	iloperidone tablets	Email	15-Nov-07	Vanda sends FDA Protocol 3101
22-192	iloperidone tablets	Telephone Call	15-Nov-07	FDA requests a copy of Protocol 3101
22-192	iloperidone tablets	Email	13-Nov-07	FDA request for additonal pharmacology information
22-192	iloperidone tablets	Telephone Call	8-Nov-07	Vanda provides IRB used for Study 3101
22-192	iloperidone tablets	Email	16-Oct-07	Vanda provides FDA CMC information requested on 15-Oct-07
22-192	iloperidone tablets	Email	15-Oct-07	Vanda requests clarity to 15-Oct-07 CMC request
22-192	iloperidone tablets	Email	15-Oct-07	FDA request for additional CMC information
22-192	iloperidone tablets	Telephone Call	15-Oct-07	FDA call about material sent on 15-Oct-07

22-192	iloperidone tablets	Email	15-Oct-07	FDA acknowledges receipt of CMC information
22-192	iloperidone tablets	Email	15-Oct-07	Vanda provides FDA CMC information requested on 11-Oct-07
22-192	iloperidone tablets	Email	11-Oct-07	FDA requests CMC information
22-192	iloperidone tablets	Email	27-Sep-07	FDA acknowledges NDA submission
22-192	iloperidone tablets	Email	27-Sep-07	Notify FDA of NDA 22-192 submission